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Original Articles

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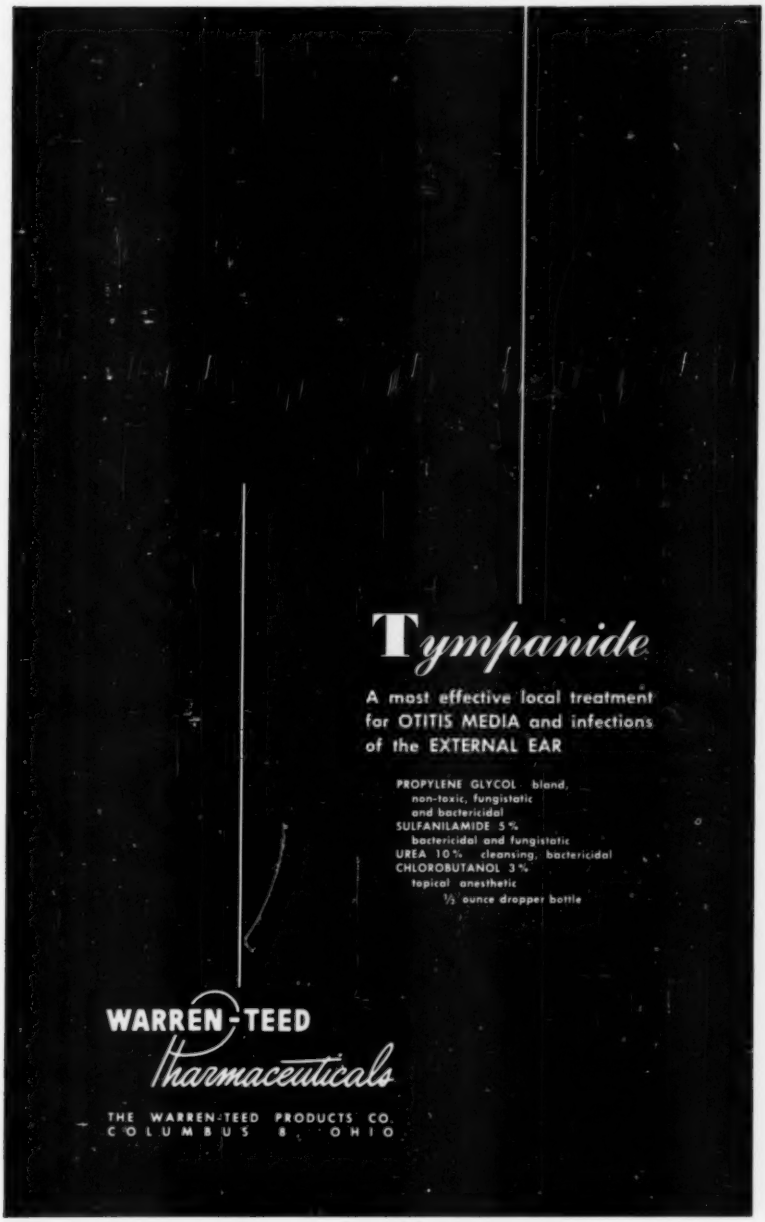
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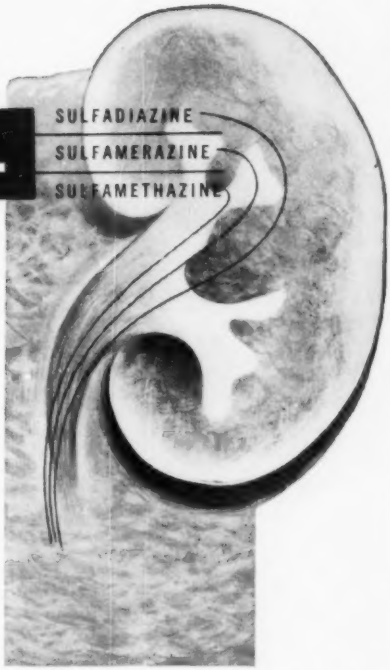

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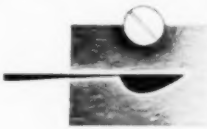

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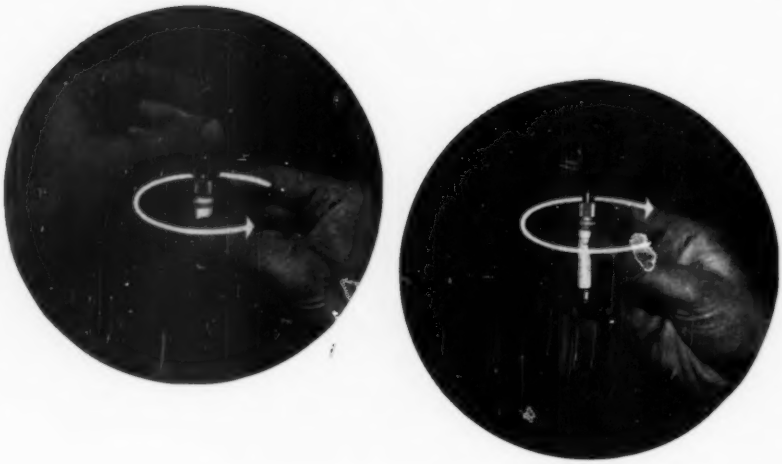

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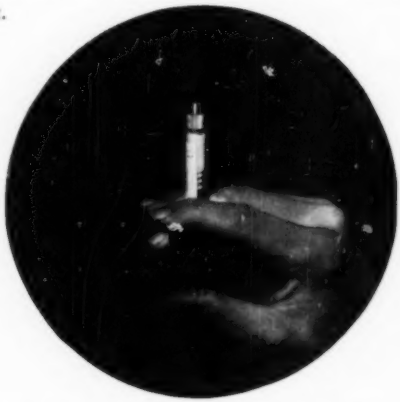

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BULLETIN OF
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JANUARY 1950

ADVANCES IN THE DIAGNOSIS OF VIRUS INFECTIONS*

FRANK L. HORSFALL, JR.

Member, The Rockefeller Institute for Medical Research, New York

THE interests of the patient, the physician, and the people as a whole are forwarded by precise diagnosis of infectious diseases. Precision in diagnosis may offer to the patient the possibility of significant modification of his illness through the use of effective therapeutic measures; to the physician an open door to beneficial management of the illness, in certain instances to specific chemotherapy, and often to control of spread of the infection to other persons; to the people the possibility of findings of ecological importance and an increase in understanding of the basic processes of infectious disease which forwards knowledge.

In the case of infections caused by viruses the dimensions of the problem of precise diagnosis are large.[1,2] In part this is because of the great multiplicity of viral agents which induce disease in man but more importantly it is a result of the difficulties encountered in identifying viruses or demonstrating antibodies directed against them in the laboratory. In the present discussion rickettsiae will be considered with viruses and no attempt will be made to distinguish sharply between rickettsial infections and viral infections. It is simpler to handle the large and

* Presented October 21, 1949 in the Graduate Fortnight Series of The New York Academy of Medicine.

heterogeneous group of obligatory intracellular parasites in this way than to break it up into arbitrary subdivisions as is now often done. Considering rickettsiae and viruses as a single large group has the further advantage that it serves to underline the obvious heterogeneity of these infectious agents. Viruses, and rickettsiae too, possess very few properties in common and their differences rather than their similarities are striking. No fewer than 60 different viruses and rickettsiae are known to cause disease in man.[3] The incidence of such illnesses is enormous and no human being escapes infection with certain of these agents. One need mention merely the common, almost universal exanthemata of childhood and the various acute infections of the respiratory tract which beset both children and adults to appreciate the frequency with which viruses cause disease. The inadequacy of available therapeutic measures for the effective management of most viral diseases is evident, but there are some indications that in the not distant future more and more of these illnesses may come to be controllable by chemotherapeutic substances.

Precision in diagnosis of viral and rickettsial diseases has resulted in recent times in the delineation of a number of entities which went undiagnosed in the past. As example, Q fever, mumps meningoencephalitis, rickettsialpox, and, of most recent discovery, infections with Coxsackie viruses come to mind. Each of these conditions presents problems of importance to physicians in the Metropolitan Area as elsewhere. The two rickettsial diseases, Q fever and rickettsialpox, in all probability can be effectively controlled by the early administration of the recently developed chemotherapeutic substances, aureomycin or chloromycetin. In each instance, as too with other viral and rickettsial diseases, a precise diagnosis is dependent in the main upon evidence obtained through laboratory procedures.

Principles of diagnosis of viral and rickettsial infections are not different from those long established for other infectious diseases. In contrast to the objectives of diagnosis in other fields of medicine more is desired in infectious diseases than the recognition and identification of the illness. The major objective is to determine the nature of the etiological factor, information which can be got only rarely in illnesses of other origin. From the clinical picture alone, given sufficient experience, it is often possible to reach a presumptive diagnosis in a number of infections of viral cause, but in the end a positive diagnosis rests in

TABLE I—TIMES DURING WHICH SPECIFIC DIAGNOSTIC PROCEDURES YIELD POSITIVE RESULTS IN VIRAL DISEASES.

Stage of disease	*Virus demonstrable with appropriate specimen*	*Specific antibody response demonstrable with serum specimens*
Incubation period	Rarely	
Prodromal period	Rarely	
Onset	Often	
Acute phase	Generally	Rarely
Recovery phase	Rarely	Often
Convalescence	Very rarely	Generally

most instances on adequate laboratory evidence. As example, it would be an extraordinarily clever physician who, on the basis of the clinical pictures, could distinguish between influenza A, influenza B, Venezuelan equine encephalomyelitis, and Rift Valley fever, to mention but a few. Similarly, the differences in the clinical manifestations of psittacosis, Q fever, and so-called primary atypical pneumonia are not sufficiently definite to make much more than a possible guess as to which of the three is present. Each of the seven infectious diseases mentioned can be differentiated readily given adequate laboratory data, but the success of this venture is often dependent upon the suspicion of the physician—upon the early suspicion—that a viral infection is present. To provide the laboratory worker with the specimens necessary for establishing a diagnosis requires that appropriate specimens, often no more than specimens of serum, be obtained early in the course of the infection, the earlier the better.

The diagnostic procedures which are used by laboratory workers for the specific identification of a viral or rickettsial infection are of but two sorts: (1) identification of the etiological agent itself, and (2) demonstration of an immune response against the agent. To accomplish either it is of the greatest importance that the possibility of viral infection be suspected early in the course of the disease so that appropriate specimens may be obtained for study. In Table I an attempt has been made to show why time is an important variable in this matter and why the physician should allow as little of it as possible to pass before adequate specimens are obtained and stored for possible investigation. The

order of frequency with which a virus can be demonstrated in most viral infections with an appropriate specimen obtained at various stages of the infection is indicated. In the great majority of instances the agent can only be demonstrated satisfactorily during the acute phase of the disease. In numerous instances the virus can be demonstrated at the time of onset of illness. It is present regularly during the early febrile period but only rarely does the agent persist into the recovery phase. The demonstration of a specific antibody response always is best carried out with at least two serum specimens of which the first should be obtained as early as possible after onset at a time when antibodies have not yet appeared in increased concentration in the blood and the second either early in the recovery phase or during early convalescence at a time when antibodies generally will have developed. In most instances antibodies are demonstrable two weeks after onset. In some viral infections their presence can be revealed as early as one week after the development of the illness. Only rarely is it necessary to wait until three or more weeks have passed in order to obtain positive results.

Depending on the nature of the infection, a virus may be identified in one or another fashion. Simplest, of course, is to visualize the virus directly as can be done with the larger, for example, those causing psittacosis, lymphogranuloma venereum, trachoma, or inclusion conjunctivitis. In other instances it is possible to identify the presence of specific antigens characteristic of the virus, an important procedure in establishing a diagnosis of smallpox or vaccinia. In still other cases it is necessary to recover the virus itself and then to identify it, which in all cases requires the use of experimental animals. A specific immune response can be demonstrated in various ways. The procedure of choice depends upon the nature of the infection. Simplest are those procedures which can be carried out *in vitro*, for example, hemagglutination inhibition and complement fixation techniques. Recent discoveries have made it possible to demonstrate a specific antibody response with considerable ease in a number of viral infections and the time is not far distant when any well-equipped hospital will be able to provide laboratory facilities suitable for the specific diagnosis of a number of the more common viral infections.

It is obvious that, if a definite diagnosis is best to serve the interests of both the patient and the physician, it should be arrived at as early as possible during the course of the illness. In a number of instances

TABLE II—DISEASES IN WHICH A SPECIFIC ETIOLOGICAL DIAGNOSIS MAY BE MADE DURING THE ILLNESS.

Disease	*Minimum time required*	*Diagnostic procedure*
	days	
Smallpox	4-7	Complement fixation (vesicle fluid).
Vaccinia	4-7	Complement fixation (vesicle fluid).
Psittacosis	8-13	Complement fixation (serum).
Lymph. gran. ven.	7-40	Complement fixation (serum).
Influenza A, or B	2-4	Recovery of virus (throat washing).
Mumps	4-6	Recovery of virus (saliva).
Herpes simplex	3-7	Recovery of virus (vesicle fluid).
Trachoma	—	Inclusion bodies (follicle).
Inclusion conjunct.	—	Inclusion bodies (epithelium).
Typhus, epidemic	5-14	Complement fixation (serum).
Typhus, murine	5-14	Complement fixation (serum).

present methods make it possible to establish a specific etiological diagnosis during the acute phase of viral diseases. Conditions in which this end can be achieved are enumerated in Table II. Of the 12 diseases named, it will be apparent that, given ideal conditions, a precise diagnosis can be established in a number during the first week of illness and that in most, a diagnosis can be made before the end of the second week. In the case of smallpox, vaccinia, influenza A, influenza B, mumps, and herpes simplex, it is often possible to establish the nature of the etiological agent within but a few days of the onset of the illness. In smallpox this is obviously of the greatest importance and whenever the possibility of this infection is suspected, vesicle or pustule fluid should be obtained at the earliest opportunity and sent immediately to a laboratory equipped to carry out complement fixation tests with immune sera. In both smallpox and vaccinia vesicle fluid contains a sufficient quantity of antigenic material characteristic of the virus so that positive complement fixation tests can be obtained directly with known immune serum. With psittacosis and lymphogranuloma venereum an antibody response is sought and, as has been mentioned, it is important to have at least two serum specimens for such determinations. In lymphogranuloma venereum the cutaneous reaction known as the Frei test is a simple and useful diag-

nostic procedure; the antigen is available from commercial sources. The Frei test is somewhat less reliable than the demonstration of an antibody response by the complement fixation procedure.

Altough with most viral diseases the recovery and identification of the etiological agent in experimental animals is a long and complex process, this is no longer true in the case of influenza A, influenza B, and mumps. Modern procedures for the recovery of these viruses are relatively simple and do not require extensive training or great skill. Because influenza viruses reach high concentrations in fluids of infected chick embryos within a day or two after inoculation, it is possible with the hemagglutination procedure to establish the presence of the agent and its identification in a relatively short time. With trachoma and inclusion conjunctivitis a specific diagnosis can be made on the basis of the morphological characteristics of the virus particles or elementary bodies in infected cells obtained from the surface of the eye. This procedure requires considerable experience but in the hands of highly trained personnel a positive diagnosis can be established readily. A skillful microscopist also may be able to establish the diagnosis in psittacosis and lymphogranuloma venereum by visualization of the elementary bodies of the virus. With typhus fever, either epidemic or murine, an antibody response is sought and in this instance, as in the case of infections due to agents of the psittacosis group, two serum specimens are of importance. When the complement fixation technique is properly carried out and with appropriately specific antigens, a distinction can be made fairly early in the course of the disease between typhus fevers due to each of the rickettsial agents which are associated with these syndromes.

With viral diseases other than those enumerated in Table II it is necessary to wait for the establishment of a specific diagnosis until recovery has begun or convalescence has set in. This is because the procedures necessary for the recovery of the agent are so time consuming and complex as to make it quicker and easier to obtain specific evidence by serological tests. There are three commonly used procedures by which a specific antibody response may be demonstrated in viral infections. In decreasing order of complexity they are: 1) hemagglutination inhibition tests with the virus *in vitro*, 2) complement fixation tests with the virus antigen *in vitro*, and 3) neutralization of the infectivity of the virus *in vivo*.

TABLE III—DISEASES IN WHICH A SPECIFIC ANTIBODY RESPONSE MAY BE DEMONSTRATED BY HEMAGGLUTINATION INHIBITION WITH THE VIRUS *IN VITRO*.

Disease	*Specimens required*
Influenza A	Acute phase and convalescent sera
Influenza B	Acute phase and convalescent sera
Mumps	Acute phase and convalescent sera
Newcastle disease	Acute phase and convalescent sera

Typical results

Serum	Serum dilution					Titer
	1:10	1:20	1:40	1:80	1:160	
Acute phase	0	+	+	+	+	1:10
Recovery phase	0	0	+	+	+	1:20
Convalescent	0	0	0	0	+	1:80

+ = hemagglutination, 0 = inhibition.

It is not our purpose here to dwell unnecessarily upon the details of the technical procedures employed to carry out serological tests appropriate for the precise diagnosis of viral infections. Nonetheless, certain information regarding them makes the interpretation of results far more comprehensible for the physician. In Table III are enumerated those diseases in which a specific antibody response may be demonstrated by the simplest procedure so far devised, the hemagglutination inhibition test. This test makes use of the fact that certain viruses cause visible agglutination of chicken or human erythrocytes. Antibodies against the virus combine with the agent and prevent it from reacting with red blood cells. This is termed inhibition of hemagglutination. In the case of influenza A, influenza B, mumps and infections with Newcastle disease virus, an antibody response may be demonstrated in a matter of but a few hours if appropriate acute phase and convalescent sera are made available. Typical results which are commonly obtained in hemagglutination inhibition tests of this kind are shown in the lower part of Table III. It is to be pointed out that because many normal persons possess circulating antibodies against certain viruses, presumably

TABLE IV—DISEASES IN WHICH A SPECIFIC ANTIBODY RESPONSE MAY BE DEMONSTRATED BY COMPLEMENT FIXATION WITH THE VIRUS ANTIGEN *IN VITRO*.

Disease

Encephalitides:—	Lymphogranuloma venereum
St. Louis	Colorado tick fever
Japanese B	Typhus: epidemic, murine, scrub
Equine:—western, eastern, Venezuelan	Q fever
Lymphocytic choriomeningitis	Rocky Mountain spotted fever
Psittacosis	Rickettsialpox

Typical results

Serum	Serum dilution					Titer
	1:10	1:20	1:40	1:80	1:160	
Acute phase	+	0	0	0	0	1:10
Convalescent	+	+	+	0	0	1:40

+ = fixation of complement. 0 = no fixation.

as a result of prior experience with them, it is always of importance to demonstrate an increase in the concentration of antibodies temporarily associated with the illness if unequivocal evidence is to be obtained as to the nature of the disease. In order best to do this, it is essential that a serum specimen be taken at the earliest opportunity, preferably not later than the 3rd to the 5th day from onset, so that this specimen may be compared directly with other serum specimens obtained from the same patient during the recovery phase or in convalescence. A twofold increase in the antibody titer of the convalescent serum over that shown by the acute phase serum is seldom considered to be of significance. A fourfold or greater increase in titer is generally to be relied upon and can be taken as evidence that a specific antibody response against the agent employed has occurred. Such a result provides a strong indication that infection by the agent in question has been sustained. Materials suitable for carrying out hemagglutination inhibition tests can be obtained from commercial sources and have proven to be satisfactory. Serological tests of this sort are relatively simple to perform, easier in

fact than the Wassermann reaction, and could be carried out in almost any well-equipped hospital laboratory.

There are a large number of viral infections in which a specific antibody response is best demonstrated by means of the complement fixation reaction with the virus antigen *in vitro*. These diseases are enumerated in Table IV. It will be noted that they include that numerous group, the various viral encephalitides, infection with certain members of the psittacosis-lymphogranuloma venereum group of agents and all of the rickettsial infections. In these illnesses it is of great importance that at least two serum specimens be made available to the laboratory which is to carry out the desired serological reaction. As with sera which are to be used in hemagglutination inhibition tests, those for complement fixation tests should include an early specimen obtained as soon after onset as may be which serves as a control for subsequent specimens taken during recovery and in convalescence. Sera should be separated from the clot promptly, must be sterile, and are best kept refrigerated. Whenever feasible, they should be transported under refrigeration and sent to the laboratory as promptly as possible. Results which are typical of those often obtained in complement fixation tests are shown in the lower part of Table IV. The example illustrated reveals a fourfold increase in antibody titer which is generally considered to be significant and indicative of the nature of the disease. To carry out complement fixation reactions with viral or rickettsial antigens requires somewhat more experience and proficiency than is needed for hemagglutination inhibition tests, but the principles involved are not different from those of the well-known Wassermann reaction. Many laboratories which do not yet carry out such tests could do so without great effort. In a number of instances satisfactory viral or rickettsial antigens can be obtained from commercial sources and these have proven to be satisfactory.

In some viral diseases *in vitro* tests have not yet been developed and the only way in which a specific antibody response can be demonstrated is by means of neutralization of virus infectivity in experimental animals. This is a complex, costly, and time consuming procedure which cannot be recommended for routine use although it remains of enormous importance to research. In Table V the viral diseases in which a specific antibody response can be demonstrated only by means of the neutralization technique are enumerated. It should be emphasized that with

TABLE V—DISEASES IN WHICH A SPECIFIC ANTIBODY RESPONSE MAY BE DEMONSTRATED BY NEUTRALIZATION OF THE VIRUS *IN VIVO*.

Disease	*Comment*
Poliomyelitis	Of limited usefulness
Yellow fever	
Herpes simplex	
Epid. keratoconjunctivitis	
Rift Valley fever	
Dengue	In developmental stage
Pretibial fever	In developmental stage
Infections with Coxsackie viruses	In developmental stage

Typical results

Serum	Serum dilution					Titer
	1:10	1:20	1:40	1:80	1:160	
Acute phase	S	D	D	D	D	1:10
Convalescent	S	S	S	S	D	1:80

S = survived. D = died.

poliomyelitis even the neutralization procedure is of limited usefulness and cannot be relied upon to give unequivocal evidence. With dengue and pretibial fever the neutralization test is not yet beyond the development stage. This is true also in that recently discovered group of illnesses designated as infections with Coxsackie viruses. When it is essential that neutralization tests be carried out, and when it has been possible to enlist the wholehearted coöperation of a trained investigator, it is important that he be supplied with acute phase and with convalescent sera just as is the case with those conditions in which *in vitro* serological tests can be performed. The results of a representative test are shown in the lower part of Table V. An eightfold increase in antibody titer is illustrated. Interpretation of neutralization tests is a problem for the investigator who carries them out. However, it can be said that in general a significant increase in antibodies is dependent, as with the *in vitro* tests mentioned above, upon the demonstration of at least a fourfold increase in antibody titer. Often far greater increases are demonstrable and serve merely to increase the reliability of the finding.

TABLE VI—DISEASES IN WHICH THE VIRUS MAY BE RECOVERED FROM THE BLOOD.

Viremia commonly present	
Yellow fever	Venezuelan equine encephalitis
Smallpox	Colorado tick fever
Lymphocytic choriomeningitis	Measles*
Typhus: epidemic, murine, scrub	Dengue*
Rocky Mountain spotted fever	Pretibial fever*
Q fever	Rubella†
Rickettsialpox	Infectious hepatitis†
Rift Valley fever	Phlebotomus fever†
Viremia rarely present	
Mumps	Western equine encephalitis
St. Louis encephalitis	Eastern equine encephalitis
Japanese B encephalitis	

* Transmissible with difficulty in animals.
† Transmissible only to man.

In a considerable number of viral infections the virus is present in and may be recovered from the blood. It should be pointed out, however, that in numerous other viral infections viremia is either not present or is so rare as to be difficult of demonstration. Those diseases in which the virus may be recovered from the blood are enumerated in Table VI. In the upper section of the table are shown the names of those conditions in which viremia is commonly present. It will be noted that in three instances, measles, dengue, and pretibial fever, it is very difficult to demonstrate the virus in experimental animals and that in three further instances, rubella, infectious hepatitis, and phlebotomus fever, there are no susceptible experimental animals known and, if the virus is to be demonstrated, this can be accomplished only by transmission to human beings. With the diseases enumerated in the lower part of Table VI viremia is but rarely present and, if an attempt is to be made to recover the agent, specimens other than blood are preferable. Whenever blood is submitted to a laboratory with the hope that a viral agent may be recovered from it, it is of great importance that discussions be held with

TABLE VII—DISEASES IN WHICH THE BLOOD IS NOT A USEFUL SOURCE OF VIRUS.

Disease	*Usual source of virus*
Poliomyelitis	Stool, nasopharynx
Infections with Coxsackie virus	Stool, nasopharynx
Influenza A, or B	Nasopharynx
Measles	Nasopharynx
Psittacosis	Sputum
Q fever	Sputum
Mumps	Saliva
Rabies	Saliva
Lymphocytic choriomeningitis	Spinal fluid
St. Louis encephalitis	Spinal fluid

the investigator who is to carry out the experiments before the specimen is obtained. The stability of viruses, the period at which they are most likely to be present and their concentration, vary enormously from one disease to another. Moreover, the conditions under which potentially infectious specimens should be transported to a laboratory are different depending on the nature of the infectious agent. Much time and effort can be saved and a far higher frequency of successful results achieved if the laboratory worker is permitted to make recommendations as to the manner of obtaining a specimen and the procedure by which it can be transported.

Those diseases in which the blood is not a useful source of virus are enumerated in Table VII, and the usual source of virus in these various conditions is indicated. It will be apparent that it is more often desirable to obtain a virus from a patient with one of the diseases shown in this table than it is with those shown in Table VI. As was indicated earlier, it is not now particularly difficult to recover a virus from a case of influenza A, influenza B, or mumps, but with the other diseases shown in Table VII somewhat greater difficulty is experienced because of the need for costly or difficultly obtained experimental animals. Recovery of poliomyelitis virus from either the stool or the nasopharynx usually requires the use of monkeys. Only in occasional instances is it possible to infect mice with strains of poliomyelitis virus and such strains are

TABLE VIII—DISEASES IN WHICH PROCEDURES FOR SPECIFIC ETIOLOGICAL DIAGNOSIS ARE NOT AVAILABLE.

Disease	*Nonspecific serological tests which are useful*
Infectious mononucleosis	Sheep RBC agglutination
Primary atypical pneumonia	Cold hemagglut.; Strep. MG agglut.
Infectious hepatitis	
Common cold	
Measles	
Rubella	
Varicella	
Exanthem subitum	
Phlebotomus fever	
Herpes zoster	

now classified as belonging to the Lansing group. Recent work has demonstrated clearly that there are at least three immunological types of poliomyelitis virus which fail to show cross immunity in monkeys. If these results have bearing on the disease in man, it becomes probable that infection with one type of poliomyelitis virus may not be followed by immunity to infection with other known types. The recently discovered infections with Coxsackie virus merit some comment. It begins to be evident that these agents may be of considerable importance and responsible for a number of previously undiagnosed syndromes in man. The first of the Coxsackie viruses was discovered in 1948.[4] The results obtained have been confirmed not only in various parts of this country but also in France and in Sweden. It appears that these viruses are widely distributed. The agents were obtained first from patients diagnosed as poliomyelitis. Other viruses belonging to the same group have been recovered subsequently from various clinical syndromes. There has not yet been sufficient work with these new viruses to make it possible to determine the frequency with which they infect man or to delineate the clinical syndromes which they are capable of inducing. The host range of the Coxsackie viruses is exceedingly limited. The only species which appear to be susceptible are suckling mice and suckling hamsters. This fact has seriously limited studies with the agents. How-

ever, there is evidence that a number of distinct immunological types occur and these fail in experimental animals to show cross immunity.

In Table VIII are enumerated ten diseases, each thought to be of viral cause, in which procedures for specific etiological diagnosis are not yet available. In two instances, infectious mononucleosis and primary atypical pneumonia, non-specific serological tests have been developed which are of some usefulness in indicating diagnosis. About 60 per cent of patients with infectious mononucleosis develop so-called heterophile antibodies which can be demonstrated in agglutination tests with sheep red blood cells. The frequency with which such antibodies are present is greatest during the second week after onset of the illness and, although the characteristic blood picture is an important diagnostic criterion, the sheep cell agglutination test provides strong confirmatory evidence for the diagnosis when it becomes positive. The serum of most normal persons and patients with serum sickness contain sheep cell agglutinins in fairly high titer. These can be removed readily by appropriate absorption techniques employing guinea pig kidney. When sheep cell agglutination tests are carried out with properly absorbed and untreated sera, a reasonably reliable indication can be obtained as to the presence of infectious mononucleosis.

A proportion of patients with primary atypical pneumonia develop components in their serum which agglutinate human group O erythrocytes at 4°C. This reaction is termed cold hemagglutination and is of some usefulness in distinguishing primary atypical pneumonia from other illnesses which are associated with pulmonary consolidation. Similarly, patients with this illness often develop antibodies which cause agglutination of a single species of non-hemolytic streptococci designated streptococcus MG. Both cold hemagglutinins and streptococcus MG agglutinins begin to appear during the third or fourth week after the development of the disease. On the average, only about 50 per cent of patients develop the components responsible for either reaction and, as a consequence, although a positive test is strong confirmatory evidence for the diagnosis, negative tests do not exclude the presence of the illness. A word of caution regarding the handling of blood specimens for cold hemagglutination tests is in order. Blood should not be refrigerated after it is obtained because the patient's erythrocytes can absorb the component responsible for the reaction and thereby lead to a false negative test. Serum should be separated from blood which has

TABLE IX—DISEASES IN WHICH CHEMOTHERAPEUTIC SUBSTANCES CAN BE EXPECTED TO YIELD FAVORABLE RESULTS.

Disease	*Chemotherapeutic substance*			
Lymphogranuloma venereum	Sulfonamides	—	Aureomycin	Chloromycetin
Trachoma	Sulfonamides	Penicillin	—	—
Psittacosis	—	Penicillin	Aureomycin	Chloromycetin
Inclusion conjunctivitis	Sulfonamides	—	—	—
Typhus, epidemic	—	—	Aureomycin	Chloromycetin
Typhus, murine	—	—	Aureomycin	Chloromycetin
Typhus, scrub	—	—	Aureomycin	Chloromycetin
Rocky Mountain spotted fever	—	—	Aureomycin	Chloromycetin
Q fever	—	—	Aureomycin	Chloromycetin
Rickettsialpox	—	—	Aureomycin	Chloromycetin

been kept at room temperature or in the incubator. If the blood is inadvertently cooled, it is possible to release the component from the red cells by warming the specimen at 37°C. for an hour or two. With the other eight diseases enumerated in Table VIII there are at the present time neither specific nor non-specific laboratory procedures which are helpful in establishing a precise diagnosis.

It has become fairly common practice to employ modern chemotherapeutic substances in undifferentiated illnesses which bear the marks of association with one or another infectious agent. There is a tendency toward the idea that a failure to obtain a strikingly beneficial result is in itself suggestive evidence for the presence of a viral infection. Attempts to confirm a diagnosis of a viral disease by this means appear undesirable and the procedure cannot be recommended. Numerous publications in the lay press and elsewhere have appeared during the past year or two which suggest that chemotherapeutic substances are now available which are useful in the treatment of viral infections in general. On careful analysis of these claims some interesting facts come to light. There are now available effective chemotherapeutic agents which appear to be definitely beneficial in four viral and six rickettsial infections. These diseases are enumerated in Table IX, and the chemotherapeutic substances which can be expected to yield favorable results

are indicated. In a number of instances trials in human beings have not yet been carried out but, on the basis of results obtained in experimental animals, there is reason to think that the substances indicated may be effective. It should be recalled that effective chemotherapeutic substances have been available for some viral diseases for a number of years. As early as 1938 it was shown that sulfonamides were effective in the management of lymphogranuloma venereum[5] and trachoma.[6] Inclusion conjunctivitis was shown to be curable with sulfonamide therapy in 1941.[7] With psittacosis effective chemotherapy with penicillin was demonstrated in 1947.[8] A few cases have been treated recently with aureomycin and definitely beneficial results have been reported. Among viral infections other than these four, however, unequivocal evidence has not been obtained that presently available chemotherapeutic substances are of definite benefit. Numerous studies have been made on the effects of aureomycin therapy in primary atypical pneumonia. Workers in this field appear to be of two minds and, although some have reported a reduction in the duration of fever,[9] others have failed to obtain any significant modification of the illness.[10]

Far more striking have been the astonishing successes recently obtained with aureomycin or chloromycetin in the treatment[9,11] of the six rickettsial diseases named in Table IX. Although there has not been sufficient time or material to permit the administration of these substances to a large number of cases with any of the rickettsial diseases enumerated, it appears clear from results obtained so far in Malaya, Mexico and this country that these substances are highly effective in combating any of the rickettsial infections. It is of interest that there is a striking correlation between the particle size and structural complexity of viruses and the effectiveness of available chemotherapeutic substances. All of the agents which induce the diseases shown in Table IX are of large size. Lymphogranuloma venereum, psittacosis, trachoma and inclusion conjunctivitis viruses are members of a single group of agents which represent the largest of all known viruses. Rickettsiae are larger yet. All of these agents can be visualized without great difficulty with an ordinary light microscope. On the other hand, with the medium sized and smaller viruses which cause the great bulk of viral infections, there is no good evidence that chemotherapeutic agents have yet been obtained which are useful in human beings.

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UNIPOLAR ELECTROCARDIOGRAPHY, INCLUDING INTRACARDIAC LEADS, IN THE DIAGNOSIS OF MYOCARDIAL DISEASE*

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INSTRUMENTATION

An action-current in the heart of animals was first demonstrated in 1856 by Kölliker and Müller[1] by means of a rheoscopic preparation made of the muscle and nerve of a frog. The observations were confirmed by later investigators, notably Engelmann[2] and Burdon Sanderson,[3] who used the earliest types of galvanometers. The action-current in the human heart was first recorded with the capillary electrometer by Waller in 1887.[4]

Progress in electrocardiography, as in most fields of medical endeavor, was thereafter proportional to advances made in instrumentation. The string galvanometer was described by Einthoven[5] in 1903. That it is widely used a half century later in the clinic and in the laboratory is a tribute to the precision, practicality, and versatility of this instrument. The advent of the amplifying vacuum tube[6] made it possible to record the relatively small currents arising in cardiac muscle[7] by means of several types of low sensitivity oscillographs. These have at present reached their most practical form in the "direct-writing" instrument. The principle is not new[8] but improvements in amplification and frequency characteristics have made it acceptable in a variety of clinical and investigative fields. The cathode ray oscillograph is theoretically the ideal instrument for recording potential differences, and electrocardiographs embodying its principle have been available for a good many years.[9] However, certain practical difficulties in its use have prevented its general clinical acceptance.

With a variety of instruments to choose from the clinician is often

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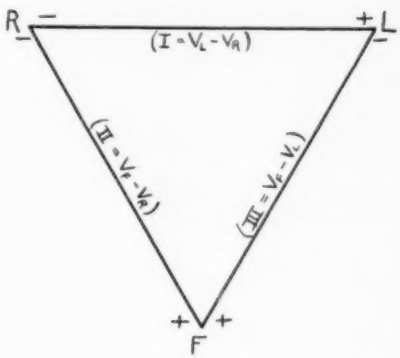

$$II = I + III$$
$$V_R + V_L + V_F = 0$$

Figure 1—Einthoven's triangle. R, L, and F are the right arm, the left arm, and the left leg which comprise the apices of the triangle. V_R, V_L, and V_F indicate the potentials of each of these extremities. I, II, and III are the standard leads, each of which is the difference in potentials between two of the three extremities as shown. The negative or positive sign at each extremity indicates the electrical conditions under which a positive deflection will result in the corresponding standard lead. The equation, II=I+III, is Einthoven's law. The sum of the potentials of the three extremities is equal to zero.

in a quandary as to which is the "best" instrument. A definition of "best" cannot be made without due consideration for the uses to which the instrument is to be put. In electrocardiographs, as in practically all instruments, certain desirable features are incorporated usually at the sacrifice of others. For example, the very practical direct recorder carries with it the disadvantage that the writing mechanism may display a variable inertia or "drag" depending on variable pressure of the writing stylus on the writing surface. If this is increased a variety of artifacts may appear in the record such as elevated or depressed S-T junctions. Further, portability requires a lightweight amplifying circuit which usually means a sacrifice of desirable high frequency characteristics. Aside from these and other purely physical characteristics such matters as cost, maintenance, availability of service, work load imposed, ruggedness, and locale of use must be considered in any intelligent appraisal of the job to be done and of the instrument to be selected.

The practitioner, therefore, who asks "What machine should I purchase?" has asked a question which is not always easy to answer satisfactorily, and may occasionally require expert analysis and weighing of many variables.

Leads and Techniques

The standard leads were first mentioned in 1906 by Einthoven.[10] In the light of the laws governing currents in volume conductors which have been called to our attention and elaborated by Wilson and his school,[11] the standard leads were really ingenious and their design indicates that Einthoven was thoroughly familiar with these physical laws. In taking these leads one of two points on the body is connected to each end of the galvanometric string or other recording device. For this reason they are called "bipolar." Einthoven called them leads I, II and III. Records of them represent respectively the difference in potential between the right arm and the left arm, the right arm and the left leg, and the left arm and the left leg (Fig. 1). Originally he made the connections between any two of the extremities and the galvanometer in such a way that an upward deflection occurred in the finished record whenever the first named extremity was electrically negative with respect to the second. This is diagramatically shown in Figure 1 where the connections between each two of the three extremities collectively make an equilateral triangle[12] universally known as Einthoven's triangle. The right and left arms and the left leg are usually indicated by the symbols R, L and F. The electrical potential or energy of each is represented by the symbol V. Using such symbols, and paying adequate attention to the sign determined by Einthoven's original, though really arbitrary, connections it is clear that lead I $= V_L - V_R$; lead II $= V_F - V_R$; and lead III $= V_F - V_L$.

Making these substitutions, it can be shown that lead II is equal to the sum of the other two leads. This relationship is known as Einthoven's law. Many attempts to disprove the law have been futile, for it depends on nothing more than an algebraic comparison of the difference in potential between two points, and between each of these and a third point.[13] Hence it is independent of all of the assumptions made in Einthoven's hypothesis,[12,14] and is indeed even independent of the shape of the triangle.

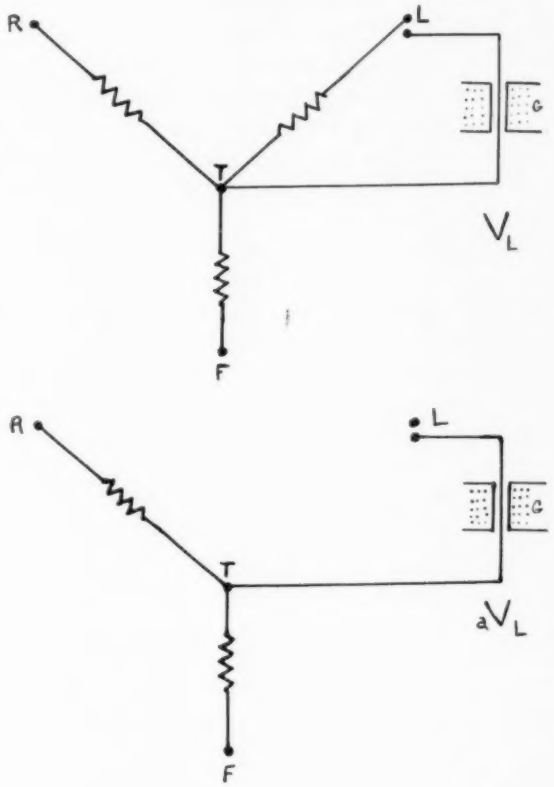

Figure 2—Upper illustration, the electrode of Wilson, Macleod and Barker connected to a galvanometer (6) for recording lead V_L. The extremities R, L, and F, are connected through equal non-inductive resistances to the central terminal T. The latter is connected to one end of the string in the galvanometer; the other end is connected to the left arm. The resulting curve is the potential of the left arm, V_L. To be noted are the separate electrodes to the left arm when an extremity lead is made with this circuit.

Lower illustration, same circuit with the direct connection between the central terminal T and the left arm broken but the indirect connection through the string intact. The resulting record of the potential of the left arm will be "augmented" by 50 per cent, and is labelled aV_L.

In making precordial leads the connections are as in the upper illustration except that one end of the string is connected to the precordium instead of to the left arm.

From these elementary considerations it must be clear that the standard leads, however useful they have been and may continue to be, have one shortcoming. Since each represents the difference in potential between two points on the body, a simple inspection of the record will not reveal with certainty the nature and magnitude of the electrical changes occurring at each of these points separately. It is true that the potential of the extremities can be calculated from the standard leads, as will be detailed later, but calculations require exact knowledge of the simultaneity of the various deflections.

Wilson, Macleod and Barker[15] were aware of the desirability of recording electrical potentials of a single point on the body when they designed the electrode which is now universally known by the senior investigator's name, or simply as the central terminal "T." The terminal was created by connecting each of the three extremities used for the standard leads to a common point through a resistor of 5000 ohms (Fig. 2). Wilson and his associates[16] were able to show by certain calculations and by experiments on a model that the potential of this electrode underwent no, or only slight, fluctuation during the cardiac cycle. A record made by connecting this electrode through a galvanometer with some point on the body was therefore a record of the uncomplicated potential variations of the point in question. In contrast to a standard lead the record was "unipolar."

Soon after this electrode was described, "lead IV" came upon the clinical scene.[17] Originally it was made by recording the difference in potential between a point on the thorax near the apex of the heart and another on the back close to the angle of the left scapula. This was, in a sense, an "asymmetrical" bipolar lead, or a "relatively" unipolar lead in which one electrode, being close to the heart, contributed potentials of considerably larger size than those contributed by the more distant electrode. In such leads the problem of determining by inspection what was occurring electrically at each electrode remained, and was perhaps more difficult than in the case of the standard leads because the electrodes were not equidistant from the source of the potential. Further, the potential of the distant electrode, as is now well known, was not "indifferent" and varied greatly between individuals and from time to time in the same patient with progressive or regressive disease of the heart.

These points somehow escaped notice or were ignored by the clin-

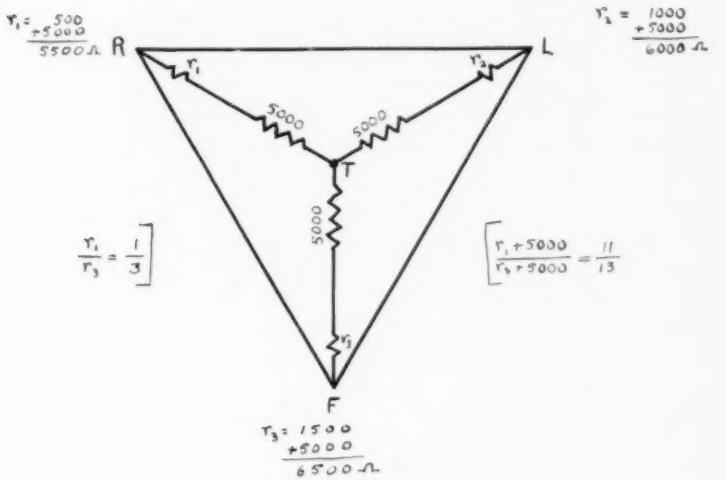

Figure 3—The central terminal and Einthoven's triangle to illustrate the equalizing effect of the 5000 ohms resistors in the three elements of the terminal. The values, r_1, r_2, and r_3, are the variable resistances, assumed to be 500 ohms, 1000 ohms, and 1500 ohms respectively, between the skin and the electrode on each of the extremities, R, L, and F.

ical investigators in the field who continued to write voluminously on the advantages to be derived from using such locations for the "indifferent" electrode as the left leg, either arm, the back, and others. The leads thus obtained were called CF, CL, CR, CB, and others, the first letter meaning "chest" and the second indicating the location of the distant electrode. After a decade and a half it has been generally agreed that the central terminal of Wilson, Macleod, and Barker is the closest approach to a zero potential electrode. It may for the present be regarded as the standard point of reference when recording unipolar electrocardiograms.

The reason for incorporating the resistances in the three arms of the Y circuit of the electrode was not apparent to many subsequent workers in the field, notably Goldberger.[18] Wilson, Macleod and Barker completely comprehended that differences would occur in the resistances between the electrode and the skin of each extremity. For example it might be 500 ohms at the right arm, 1000 ohms at the left arm, and

1500 ohms at the left leg (Fig. 3, r_1,r_2,r_3). Under such circumstances the ratio of resistances at the right arm (r_1) and the left leg (r_3) would be ⅓. The fall in voltage across the three limbs of the circuit would be unequal and the potential of the central terminal would not be zero. In order to overcome this difficulty Wilson and his associates originally used resistances of 25,000 ohms between the terminal and each extremity, but this made for practical difficulties arising from necessary loosening of the string and increased sensitivity of the recorder to stray current interference. A compromise on 5000 ohms was reached although the more desirable larger resistors may possibly be used with electrocardiographs of the future.

It is to be noted that when 5000 ohms of resistance are placed in series with each extremity, the values r_1, r_2, and r_3 become 5500, 6000, and 6500 ohms respectively. The ratio of the resistances in the limbs of the circuit to the right arm and to the left leg is reduced to 11/13. In short, the resistors tend to equalize differences in conductivity of the skin under the electrodes. Failure to use them, as in Goldberger's electrode, has been shown theoretically[19] and experimentally[20] to result in errors of considerable and variable magnitude. For this reason the use of Goldberger's modification of Wilson's central terminal is not an acceptable technique in unipolar electrocardiography.

There has been some confusion as to terminology of leads. When a record is made by pairing some point on the body with the central terminal T, the record is a "unipolar" lead from that point. Hence, depending on the location of the "exploring" electrode there may be unipolar extremity leads, precordial leads, esophageal leads, intracardiac leads, and others. The term "unipolar" applies to a technique and not to any specific location of the exploring electrode. With the general acceptance of Wilson's electrode the term may eventually become superfluous.

Extremity Potentials

A record of the difference in potential between the terminal T and any of the extremities R, L, or F, is called a unipolar extremity potential or lead. These leads were originally made for the purpose of analyzing the components of the bipolar standard leads. Normal values were worked out as long ago as 1935.[21] In the early clinical application of them it was demonstrated that the Q wave of lead I or of leads II and

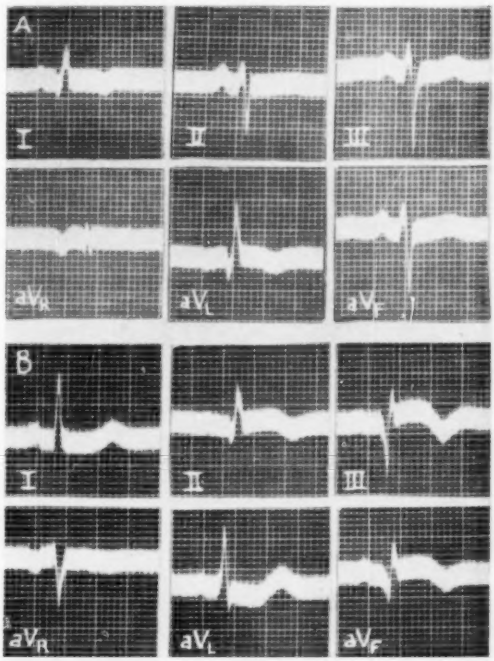

Figure 4, A.—Recent "lateral" infarction of the ventricular myocardium. Lead aV_L is a semidirect lead from the area of infarction and determines the occurrence of a Q wave in standard lead I.

B.—Recent "posterior" infarction of the ventricular myocardium. Lead aV_F is a semidirect lead from the area of infarction and determines the occurrence of a Q wave in standard lead II, and of part of this deflection in standard lead III.

III in myocardial infarction resulted from the circumstance that the left arm in the former and the left leg in the latter (Fig. 4) were either partial or complete semidirect leads from the region of infarction.[22] Later Wilson, Johnston, Cotrim, and Rosenbaum[23] showed that the electrical position of the heart could be estimated from relationships between the extremity potentials and the precordial potentials. When the potential of both upper extremities simulated a lead from the right side of the precordium and the potential of the left leg was similar to a lead from the apex, the electrical position was said to be vertical (Fig. 5); when

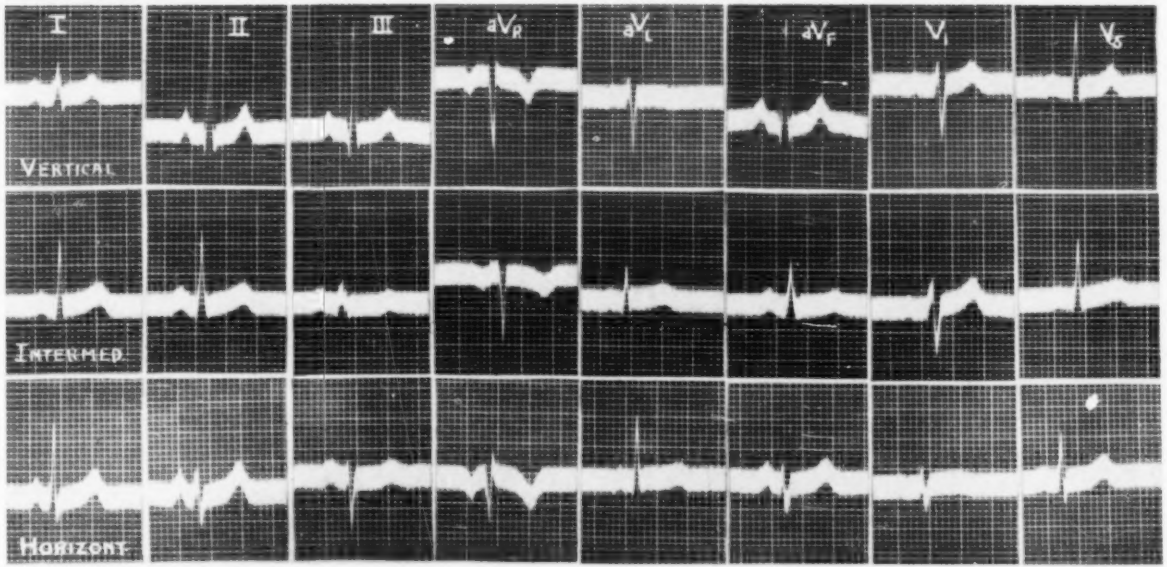

Figure 5—Electrical positions of the heart as determined by the extremity potentials. I, II, and III are the standard leads; aVR, aVL, and aVF are the augmented extremity potentials; V_1 and V_5 are precordial leads. To be noted with the vertical position is the similarity of lead aVF to leads II, III and to lead V_5; with the intermediate position the similarity of lead aVR to the inverse of leads I, II, and V_5; and with the horizontal position the similarity of lead aVL to lead I and to lead V_5.

the potential of the right arm and of the left leg simulated the right precordial lead, and the potential of the left arm and the left side of the precordium were similar, the electrical position was said to be horizontal (Fig. 5). Between these two extremes semivertical, intermediate (Fig. 5), and semihorizontal positions were described depending upon the relative electrical effects of the right and left ventricles on the left leg and the left arm.

The method has been useful in describing the electrical position of the ventricles independent of the direction of the mean electrical axis of QRS. Goldberger has elaborated on the use of the extremity potentials for determining electrical position.[24] There has been a tendency to regard the electrical and the anatomical positions of the heart as identical. Further, it has been assumed that a specific form of QRS in a record of an extremity potential means that the extremity in question has a specific anatomical relationship to a ventricular chamber, its cavity, or both. It is probable that neither of these assumptions is always fully justified, particularly in the abnormal heart. Occasionally in the latter no semblance at all can be detected between the form of QRS in the extremity leads and in the precordial leads. The principal reason for this is that the attachment of the extremities to the trunk, being relatively distant from the heart, record potentials from a considerably larger surface than do the nearer precordial electrodes.

The relations of the standard leads to the extremity potentials is such that if two of either set are known the other four may be calculated. These relationships may be expressed algebraically[25] as follows:

$$V_R = \frac{e_1 + e_2}{3}$$

$$V_L = \frac{e_1 - e_3}{3}$$

$$V_F = \frac{e_2 + e_3}{3}$$

where e_1, e_2, and e_3 are the evident potentials recorded in leads I, II, and III (Fig. 5). When the QRS deflections of leads I and II are similar in form the complexes of lead V_R resemble both but are in the reverse direction; when QRS of lead III is dominantly downward and is the inverse of lead I, the complexes of V_L are similar to those of lead I; and when the complexes of leads II and III are alike, those of lead V_F have the same form.[23]

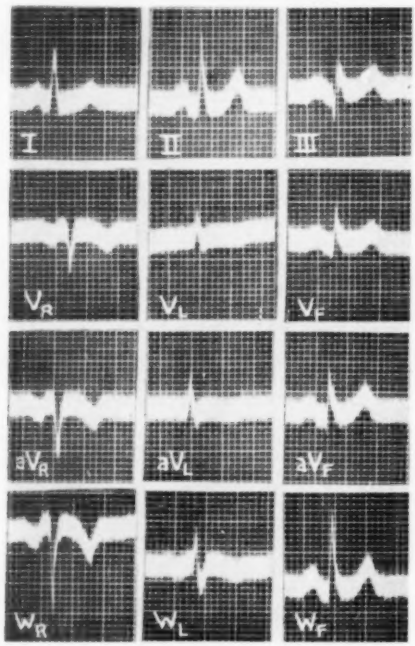

Figure 6—Standard leads (I,II,III), extremity potentials (V_R,V_L,V_F), augmented extremity potentials (aV_R,aV_L,aV_F), and "bipolar" extremity potentials (W_R, W_L, and W_F) in a patient with arteriosclerotic heart disease. It is to be noted that the size of the augmented leads is approximately 1.5 times as large, and the "bipolar" extremity leads approximately twice as large as the extremity potentials.

The extremity potentials are often inconveniently small. They may be made 50 per cent larger by the simple procedure of breaking the connection between the central terminal and the extremity being studied (Fig. 2). Such leads are said to be augmented[18] and are indicated by the symbols aV_R, aV_L, and aV_F. By simple algebra it can be shown that the values of these leads in terms of the standard leads are expressed by ratios similar to those given for the extremity potentials but the denominator in each instance is 2 instead of 3.

Recently Cohen and Glicksman[26] have pointed out that a reasonable approximation of the extremity potentials may be obtained by a bipolar

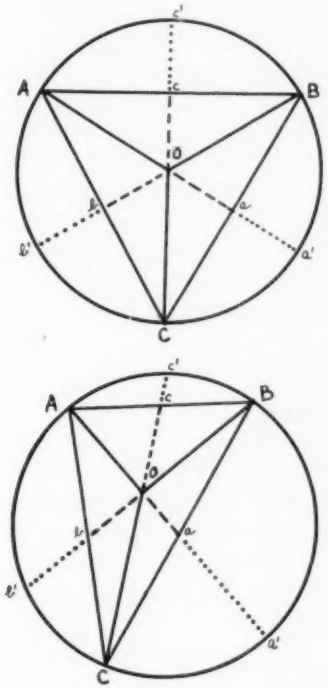

Figure 7—Geometric visualization of the validity of the principle of augmentation.

In the upper figure an equilateral triangle has been drawn in a circle. By means of it the size of deflections in lead V_R may be visualized as proportional to the length of the line AO; in lead aV_R proportional to the length of line Aa; and in lead W_R proportional to the length of the line Aa'. Similar proportions exist between the various leads from the left arm and the left leg and the length of the various subdivisions of the lines Bb' and Cc' respectively.

In the lower figure the triangle is oblique. In it the ratio of 1.5:1 still exists between the lines AO:Aa, BO:Bb, and CO: Cc. But from the eccentric location of O it is clear by inspection that Aa' is not twice the length of AO, nor is Bb' twice the length of BO, or Cc' twice the length of CO. The "bipolar" technique of recording extremity potentials is not valid unless the distance between each electrode and the source of potential is the radius of the same circle.

technique. This consists of placing one electrode on the extremity to be studied and the other on the body at a point as diametrically opposite as possible. In the case of the arms this point is in the contralateral midaxillary line approximately halfway between the apex of the axilla and the symphysis pubis; in the case of the left leg it is the submental region on the left side. Curves thus obtained are approximately twice the size of the extremity potentials obtained with the aid of the central terminal. The authors recommended that these leads be called WR, WL, and WF (Fig. 6).

These leads are important because they are easy to obtain without special equipment. Further, if they should be shown to be twice the size of the true extremity potentials in a large series of cases, this evidence would greatly strengthen the already strong position of Einthoven's hypothesis.

The relations of the extremity leads (VR,VL,VF), the augmented extremity leads (aVR,aVL,aVF), and the "bipolar" extremity leads may be represented graphically (Fig. 7). Assuming that the body is a large sphere and that Einthoven's triangle is equilateral and in the plane of a source of electrical energy at the center of the sphere (upper half of Fig. 7), then the potential of lead VR is proportional to the length of the line AO; of aVR to the length of the line Aa; and of WR to the length of the line Aa′. The ratios of AO:Aa:Aa′ and hence of VR:aVR:WR are 1:1.5:2. Similar proportionalities exist for the leads from the other two extremities. If the triangle is assumed to be oblique because of an eccentric location of the source of potential (lower half of Fig. 7), then VR and aVR are still proportional to the length of AO and Aa respectively and have a ratio to each other of 1 to 1.5. But in this figure obviously Aa′ is not twice the size of AO.

The relationships support the generally accepted contention that augmentation is independent of the shape of the triangle. However, the "bipolar" technique of recording extremity potentials is only valid if the electrodes are equidistant from the source of potential.

Precordial Potentials

Leads from the precordium differ from extremity leads principally by being closer to the surface of the heart. They will therefore yield records which have a better resemblance to direct leads taken from the subjacent surface. From this fundamental observation[27] it was obvious

that a single precordial lead could not give detailed information from the entire heart's surface, and under certain circumstances could give wholly misleading data by virtue of its incompleteness. Although this point was emphasized in normal subjects in 1935,[21] and further amplified in abnormal subjects in 1938,[22] it is only recently that the practice of recording more than one precordial lead has become general.

In a normal subject the changes which occur in the record as the exploring electrode is moved from the right sternal edge (lead V_1) to the left anterior axillary line (lead V_6) are now well known. The leads from the right side of the precordium are characterized by a small R wave, a deep S wave, and a T wave which may be in either direction but usually upright in adults (Fig. 5). The records are assumed to be similar to what would be obtained if the electrode could be placed on the epicardial surface of the right ventricle. The leads from the left side of the precordium are usually characterized by a small Q and S, and a prominent R with an upright T wave (Fig. 5). Either or both of the first mentioned deflections may be absent. The record is assumed to be similar to, but smaller than, a direct lead from the epicardial surface of the underlying left ventricle. In the mid-precordium, records are frequently obtained which have characteristics of deflections seen in leads from either side of the precordium. They are "transitional" in form, and the area on the chest from which they are obtained is called the "transitional zone."

The RS or "intrinsicoid" deflection[28] in the chest leads, analogous to the intrinsic deflection[29] in direct leads, represents the period of increasing electrical activity of underlying muscle. Its size is proportional to the size of the electromotive force developed across the ventricular wall during this period. It has been customary to measure the time of the beginning of this deflection, or the peak of the R wave, with respect to a variety of reference points.[21,30,31] Perhaps the most practical for clinical purposes is the beginning of QRS in the precordial lead concerned. The maximum normal value usually given for the interval between the beginning of QRS and the peak of the R wave in leads V_1 and V_2 is 0.03 second,[30] and in leads V_5 and V_6 0.05 second.[31] In hypertrophy of the left ventricle and in left bundle branch block the deflection is delayed in leads from the left side of the precordium; in right ventricular hypertrophy and in right bundle branch block it is delayed in leads from the right side of the precordium. In hypertrophy

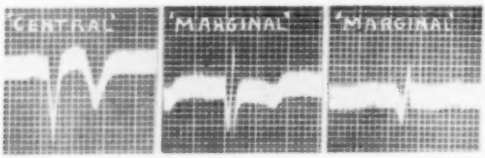

Figure 8—Principal configurations of QRS encountered in precordial and extremity leads when there is infarction of the myocardium (see text).

the delay is encountered usually when the morbidity is quite advanced and already easily detectable by clinical or roentgenologic methods, although there are exceptions particularly where the right ventricle is involved.

Although the peak of the R wave has been clinically accepted as marking the arrival of excitation at the epicardial surface of the underlying myocardium, analytical[32,33] and experimental[34,35] considerations make it obvious that activity of the muscle concerned is not completed until the end of the intrinsic deflection or the nadir of the S wave. However, in clinical records the beginning of the intrinsicoid deflection is usually easier to identify than the end, and since the error involved is probably small it will very likely continue to be interpreted as it has been in the past.

The modifications of QRS which occur in the precordial leads when ventricular infarction occurs are well known to the internist. A summary may be given by indicating that, as in the standard leads, three distinct alterations of the curve may occur. These are: 1) a modification of QRS; 2) an elevation or depression of the S-T segment; and 3) a change in the T wave.

The modification of QRS which occurs with infarction was anticipated by the theoretical and experimental studies of Wilson and his school. Actually the curves obtained clinically may be classified into two types: the "central" and the "marginal" (Fig. 8). The first is characterized by a QRS which is entirely negative, and in clinical curves usually slurred or notched. It gets its name from the fact that similar records were experimentally obtained by Wilson and his associates[27] when an electrode was placed directly over the center of an infarct. The second is characterized by a QRS which begins with an abnormally

deep or broad initial negative deflection or Q wave, to be followed by a positive deflection or R wave of variable size, and occasionally a terminal S wave. It is called the marginal type because it was obtained in the experiments referred to from the margin of the infarct.

The form of the S-T segment and T wave which will be encountered with these types will depend on a variety of factors, the most important of which is the age of the infarct. They are observed best in serial records. Occasionally myocardial infarction will be accompanied by abnormalities only in these deflections without any characteristic change in QRS.

Although the correlation between the morbidity found at necropsy with the electrophysiologic behavior of the heart during life is remarkably good, it is not perfect, and never can be. The clinician must be wary of correlative studies in necropsied cases because the disease in these patients has reached a stage sufficiently advanced to cause death. Even so, a careful reading of such studies will disclose that a considerable percentage of the patients displayed electrocardiographic abnormalities which were not diagnostic of recent or ancient myocardial necrosis. In earlier phases of the disease encountered clinically the percentage of unquestioned positive results will be even less. The point to be emphasized is that despite the newer leads considerable caution must still be exercised to avoid the pitfall of saying that a patient does or does not have myocardial infarction on the basis of the electrocardiographic findings alone. Serious errors both of exclusion and inclusion are still too often made in the clinic because of the failure of the clinician to regard the electrocardiogram as a laboratory aid which has all the shortcomings and fallacies of any such aid.

A question without a satisfactory answer at present is what number of precordial leads should be recorded. Exclusive of chest leads, it would seem desirable to take routinely either the standard leads, the extremity potentials, or both. If a choice must be made between these two, the extremity potentials are preferred because they give certain information, already discussed, over and above that which is given by the standard leads. With regard to chest leads, the clinical objective to be attained is electrocardiographic data from as much of the heart's surface as possible. The ideal procedure would be to make a complete electrocardiographic survey of the entire thorax and perhaps the upper abdomen. Obviously this would be impractical for routine work, and it is

questionable whether much of the information obtained would be of any clinical value. To say what are the best leads for every patient is impossible. It is desirable to have an electrical record from both lateral extremities of the precordium and from its middle. To this end we have for a good many years taken leads V_1, V_3, and V_5 routinely. These, considered with the extremity potentials or standard leads, usually give as much information as is needed clinically but there are exceptions. From the history it may be suspected that there are electrical abnormalities in some region of the heart not explored by the leads used. In such instances additional leads should be taken further to the left or to the right, or above or below the usual precordial stations. A satisfactory point on the back from which to make a routine lead is difficult to define because of the considerable normal variation in such leads, and the difficulties in interpretation occasioned by the effects of the variably oriented basal orifices of the heart.

Efforts to solve the problem of which leads tc take are under way, and reference to these will be made farther on.

Esophageal Leads

Esophageal leads have been extensively studied by Hurst Brown,[36] Nyboer,[37] and others.[38,39] They have been useful in the study of the electrophysiologic behavior of the left atrium since the esophagus is normally in apposition to the posterior wall of this chamber. An electrode in the esophagus at the proper level will be separated from the atrial musculature only by the pericardium and the various layers of the esophagus itself. This is usually at levels between 32.5 and 40.0 cm. from the external nares when the electrode is introduced through the nose. Leads from the atrial region are characterized by a diphasic P wave. The rapid change from positive to negative is the atrial intrinsic deflection. The QRS of this lead usually begins with a deep negative deflection ascribed to its relation to the interior of the left ventricle through the mitral orifice. It is often followed by a positive wave of variable size presumed to be caused by late activation of posterobasal left ventricular muscle. The T wave is inverted. Leads from the ventricular levels (45 to 50 cm. from the external nares) may be in the lower esophagus or stomach. Leads from these levels are from the external surface of the left ventricle and would be expected to be similar in form to a precordial lead from the apex such as lead V_4 or lead V_5.

From a practical point of view esophageal leads have been used mostly to explore the posterior and posteroinferior aspects of the left ventricle for evidence of the electrical effects caused by myocardial infarction. When present the resulting QRS may be of the central or marginal type such as described for the chest leads. Esophageal leads are also occasionally of value in the identification of an atrial rhythm.

These leads have been used for diagnostic purposes only sporadically. The reason probably is that the technical aspects are difficult, and the procedure may cause discomfort to the patient. Further, leads taken from near the interventricular sulcus are often confusing. Lastly, much of the desired information usually may be obtained more easily by leads from the surface of the body.

Intracardiac Leads

When Cournand and Ranges[40] performed the first catheterization of the heart in this country on the Third (N.Y.U.) Medical Division of Bellevue Hospital, it was immediately apparent that the method could be used to study electrical potentials developed in the interior of the heart during the passage of an action current across it. It was envisioned that in this way some puzzling aspects of electrocardiographic theory might be clarified. Our own efforts in this regard were interrupted for half a decade by the late war, but got under way in 1946 in the same room and with the same ancient fluroscope originally used by Cournand and Ranges. Meanwhile the method has been used elsewhere and numerous reports[41-47] are now available on the electrical potentials encountered in the right heart of man in a variety of abnormal conditions. Records have also been made from the cavities of the left atrium and the left ventricle. In unpublished observations, Sodi-Pallares and his associates have successfully inserted a catheter by way of the right radial artery into the left ventricle in twenty-one patients without incident.

It is not likely that the method will have any direct clinical application. However, it has been of considerable help in making certain electrocardiographic phenomena understandable, which in turn will almost certainly have a bearing on the solution of practical problems.

One of these problems has been the origin of various deflections in the normal electrocardiogram. The origin of the Q wave and of the R wave in the bipolar leads has been generally agreed upon. The former

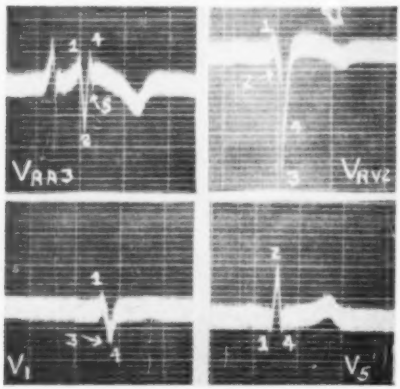

Figure 9—Leads from the cavity of the right atrium (V_{RA_3}), the cavity of the right ventricle (V_{RV_2}), and from precordial points on the borders of the precordium (V_1 and V_5) recorded at half normal sensitivity of the string (1.0 mv = 0.5 cm) in a normal subject. Deflections which occur simultaneously bear the same number. Deflection 1 is regarded as resulting from an electrical force generated during early excitation of the left side of the interventricular septum; vectorially it may be regarded as the "Q vector." Deflection 2 is regarded as resulting from excitation of the free wall of the left ventricle principally at the apex; the force involved may be regarded as the "R vector." Deflection 4 is the principal but not the only component of the final QRS depression in precordial leads and in certain standard leads; it is called the "S vector." Deflections 3 and 5 are obscured as part of deflection 4 in leads from the surface of the body.

has its origin in the left side of the interventricular septum, and the latter in the apical portions of the left ventricle. The origin of the S wave is not so clear, and the difficulties both with regard to R and S in leads from the right side of the precordium in man have not been investigated until recently.[44,48] Our findings in the usual normal subject[49] are summarized in Figure 9 in which simultaneous deflections in leads V_1 and V_5, and in leads from the cavities of the right ventricle (V_{RV_2}) and right atrium (V_{RA_3}) bear the same number.

The frequent simultaneity of the S wave in leads V_1 and V_5 (deflection 4) with a notch on the ascending limb of the S wave in the lead from the right ventricular cavity and with an R′ in a lead from the cavity of the right atrium has suggested to us that the S wave in precordial leads, or at least a major part of it, arises in some considerable

mass of muscle at the base of the right ventricle. The fact that large positive potentials with a corresponding time may be found in leads from the pulmonary artery just above the pulmonic valve support the belief. A muscle band which could easily account for the deflections under consideration does exist in the right ventricle and is known as the crista supraventricularis. Normally it is the thickest part of the right ventricle. Its mean direction of excitation seems to be to the right, upward, and probably backward although this conceivably varies with the position of the heart. Clearly there are other regions involved to give rise to such deflections as 3 and 5 which probably are included in the S wave of surface leads.

The relationship of such data to advances in diagnostic methods may not be immediately apparent. It was pointed out earlier that one of the clinical problems to be decided is the number of leads to be taken. Practical considerations make it desirable for these to be few in number and easy to interpret. Einthoven, Fahr, and de Waart[12] reduced the various ventricular deflections to a single vector in the frontal plane which was called the mean manifest potential of the ventricles and was designated by the symbol "E." Evidence has gradually accumulated to support the validity of the assumptions, known as Einthoven's hypothesis,[12] on which this procedure was based, although some dissension still exists.[50] It is not likely that a reduction of all of the electromotive forces developed during ventricular excitation to a single vector can give all of the information usually desired clinically. But it may be possible to reduce them to three principal ones corresponding to the deflections 1, 2, and 4 in Figure 8, and which may, for lack of better terminology at present, be called the "Q" vector, the "R" vector, and the "S" vector. Knowing the size and direction of each, the clinician will very likely have all of the electrical information about ventricular activation which he needs. The only problems that remain are a simple manner of recording these vectors and then of testing the validity of the statement.

The intracardiac leads have been of considerable value in solving such problems as the manner of excitation of the right side of the heart in bundle branch block; the nature of atrial circus rhythm and tachycardias; the rate of conduction in the right atrium; the nature of demarcation potentials developed as a result of pressure of the electrode on the subendocardial myocardium; and the like. Since these are at present of theoretical interest, no further reference will be made to them.

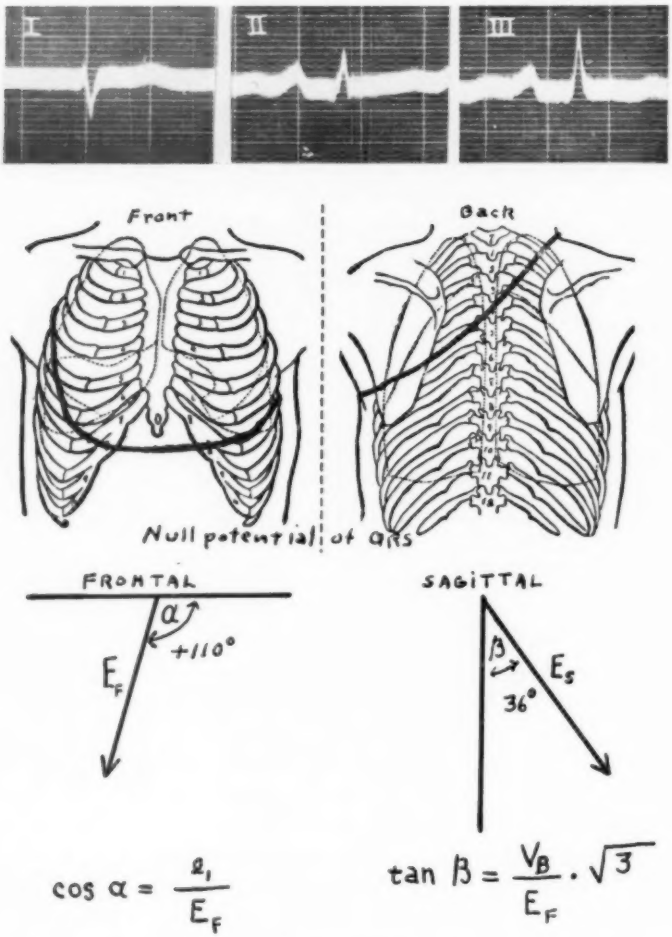

Figure 10—"Null-potentials" of QRS plotted on the thorax (solid line) of a patient with chronic cor pulmonale. The line determines a tilted plane through the thorax the inferior surface of which faces downward, to the right, and backward.

The angle alpha (angle between the horizontal and the mean manifest potential, Er, in the frontal plane) and the angle beta (angle between the vertical and the mean manifest potential, Es, in the sagittal plane viewed from the left), calculated as shown from the standard leads I, II, and III and from the potential of a point on the back at the level of the 7th dorsal spine (lead V_B, not shown), corroborates the spatial direction of the mean manifest potential determined from the surface null-potentials of QRS.

Methods of the Future

It seems appropriate in a symposium of this type to comment on methods in use at present in the laboratory which may in a short time be of practical value in the clinic.

One of these is the method of *plotting "null-potentials"* of QRS on the chest. This consists of making electrocardiograms from numerous points on the chest and abdomen, and determining those in which the algebraic sum of the area of the QRS deflections is zero. These null-potential points are then joined by a continuous line (Fig. 10). Regarding all the electromotive forces developed during ventricular electrical systole as a single vector, this continuous null-potential determines a plane through the body which is approximately perpendicular to the axis of the vector. From a consideration of the tilt of this line it is clear in the figure, for example, that the vector is pointing downward and to the right, and backward. Calculation of the direction of the vector in the frontal and sagittal planes, using Einthoven's[12] and Wilson's[51] equations, shows that the vector does in truth point downward to the right, and backward. Grant[52] has demonstrated in unpublished observations that calculations made by regarding the thorax as a cylinder are in general agreement with what is found by actual plotting of the null-potentials.

The method, though at present unwieldy, has been useful to us in studying the relative size and direction of the "Q," "R," and "S" vectors described above. It has also served to demonstrate further the validity of Einthoven's hypothesis.

A method in use for some time is *vectorcardiography*. Clinical adoption has been delayed by the inadequacy of recording devices for clinical use. The vectorcardiogram is a vector function of time. Instead of regarding QRS as a single vector, it is regarded as a vector which changes in size and direction from moment to moment and in several planes during electrical excitation of the ventricles. A line joining the tips of these vectors creates a figure which is called the vectorcardiogram. One of the drawbacks of most instruments thus far devised for making such records is that vectorcardiograms of the P, the auricular T, the QRS, and the ventricular T are superimposed. In our laboratory Dr. Briller and Mr. Marchand have succeeded in devising a method of recording each component of the vectorcardiogram separately. The method is called "differential vectorcardiography" and an example of

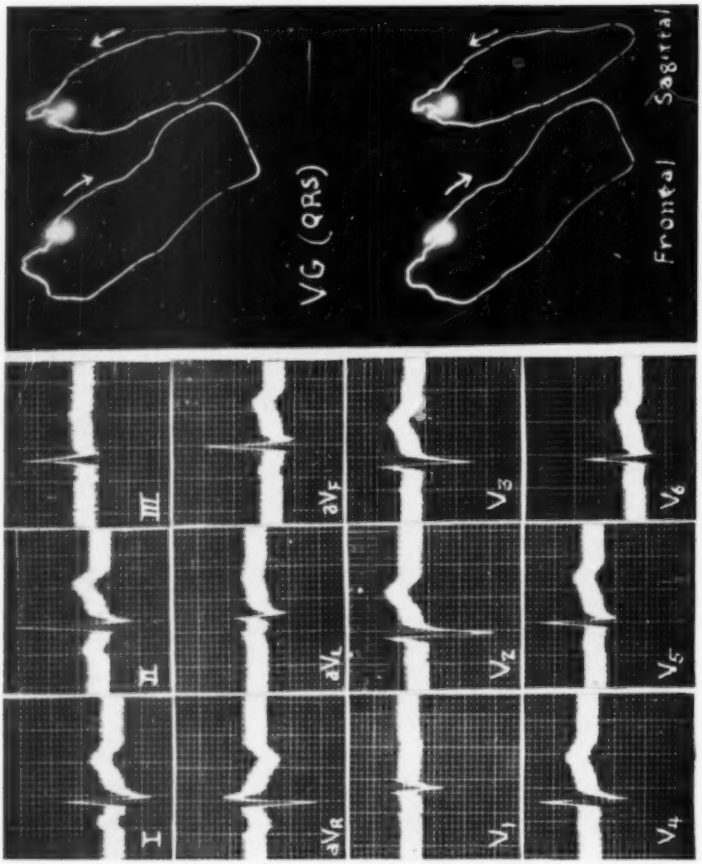

Figure 11—Differential vectorcardiography, normal subject. On the left are twelve leads frequently taken clinically in an electrocardiographic survey. On the right are two sets of frontal and sagittal vectorcardiograms of two successive cycles on the same subject. These vectocardiograms are of QRS only, and do not include the P form or T form. Time is indicated by the minute breaks in the records.

So far as QRS is concerned all the information obtained in the twelve leads at the left is incorporated in the upper or lower two records on the right.

the vectorcardiograms of QRS in the frontal and sagittal planes is shown in Figure 11. All of the twelve leads shown in the figure are thus reduced to two records so far as QRS is concerned. The calculation of areas[53] and gradients[54] can be made fairly simply from such curves instrumentally. This may prove a method of obtaining what is so badly needed in clinical electrocardiography, namely, simplicity.

A radical departure from the time honored method of recording the cardiac potential as a two-dimensional wave trace, in which one variable is time, has been suggested by the principle of radar. On the radarscope, potential may be represented by brightness rather than by the height of a deflection or length of a vector. A "map" may be made on the radarscope divided into small subdivisions so as to give what is called an "area display." Each subdivision on the scope will show variations in brightness depending upon the potential developed and picked up from the corresponding subdivision on the thoracic wall over the heart. Such a device has been designed by Goldman[55] and his associates at the Massachusetts Institute of Technology but instrumental difficulties, at this early stage, are, as always, numerous. It is likely that they will be surmounted eventually. Then the reliability and validity of the method will have to be tested clinically. Nevertheless, it represents a new approach, and its full significance to clinical electrocardiography will be determined in a matter of time.

Summary

In the late twenties it was frequently heard that there was no future in electrocardiography. After all, Einthoven had laid down the physical principles, and Lewis had done all that could be done experimentally and clinically to clarify our conceptions of the arrhythmias. To certain observers, unfamiliar with the history of progress in medical sciences, the small subdivision known as electrocardiography seemed to have reached a permanently sterile end.

The hazard of saying that any field of scientific endeavor has reached an end has been exemplified by the progress made in electrocardiography in the past two decades. The recent rapid strides in the physical sciences make it even hazardous to regard the present stage of progress in electrocardiography as the end of the beginning. A century hence it is entirely possible that the recent advances presented will be regarded as only the beginning of the beginning.

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RENAL FUNCTION TESTS IN THE DIAGNOSIS OF GLOMERULAR AND TUBULAR DISEASE*

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THE etiological diagnosis of intrinsic renal disease sometimes can be made on the basis of simple clinical observation. More often than not, however, accurate diagnosis is difficult. This is especially so when renal failure is severe, for there is nothing distinctive in the clinical picture of the terminal phase of chronic kidney diseases, no matter what the original etiology.

Evaluation of glomerular and tubular function is essential for the understanding, and thus for the proper management, of the diverse clinical problems that may arise in the course of renal disease. At times, the functional pattern may yield a clue to the correct diagnosis. Advances in our abilities to assess glomerular and tubular functions have been considerable. But they are not sufficiently definitive to give by themselves a complete diagnostic scheme. There is no doubt that the most important considerations in arriving at the proper diagnosis still include a careful history and a thoughtful study of the urinary sediment combined with a thorough knowledge of the natural histories of the diffuse renal diseases. Nevertheless, study of discrete glomerular and tubular processes has been of considerable importance to the understanding of how various diseases can affect kidney function. It is the purpose of this paper to present a way of thinking about kidney function, or more specifically, about glomerular and tubular function, that will be useful in the study and evaluation of clinical problems.

But first, it might be in order to review briefly the most important

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The examples of renal function measurements presented in this paper are selected from observations on a large number of patients with a variety of diseases. Grateful acknowledgement is expressed to Drs. Saul J. Farber, Neal J. Conan, Jr., Edmund Pellegrino and John D. Alexander who have been responsible for the performance of these studies, and to Sharp and Dohme, Inc. for a generous supply of p-Aminohippurate.

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developments that have placed renal physiology on firm ground. Slightly more than 100 years ago Ludwig[1] proposed that urine was formed by simple filtration at the glomerulus. Cushney's monograph of 1917[2] presented cogent arguments for the belief that urine formation was the result of glomerular filtration and tubular reabsorption. However, it remained for Richards and Wearn[3] to demonstrate in their classic experiments, involving actual collection of glomerular filtrate and tubular urine from frog kidneys, that this theory was indeed a fact. They and their co-workers showed that all substances in plasma, except those of high molecular weight such as the proteins, were also found in the same concentration in the glomerular filtrate. They further found that many of these substances were partially or wholly reabsorbed as the glomerular filtrate passed down the tubules. Later, similar studies were made on mammalian kidneys.[4] Several years before, Marshall had presented evidence that the renal tubules can excrete organic materials such as phenolsulphonephthalein and phenol red.[5,6] Then, largely thru the efforts of Homer Smith and his colleagues,[7] adequate indirect methods were developed for the measurement of discrete renal functions in man, such as renal blood flow, rate of glomerular filtration, and tubular functions including maximal abilities to reabsorb glucose and to excrete substances such as diodrast or p-aminohippuric acid (PAH).[8] Under ordinary circumstances the latter two values, designated TmGlucose and TmPAH, are relative measures of active tubular mass. Subsequently, these techniques were applied to the study of innumerable fundamental physiological and pharmacological problems by Dr. Smith's group and by many other investigators as well. Perhaps one of the more important results was the demonstration[7] that tubular mass is independent of variations, within limits, of glomerular filtration rate and renal blood flow. These and other data indicate that all nephra are functioning at all times in normal man under ordinary circumstances.

Very few of the ordinary tests are measures of any specific glomerular or tubular functions. Nevertheless, it is hardly necessary to state that they can be very useful in the evaluation of the functional status of patients with kidney disease. The relations between the usual clinical measurements and the discrete renal functions are shown in Table I. This listing does not include all tests. The methods for measuring specific renal functions shown in the middle column are simply those most commonly used today. The endogenous creatinine clearance

TABLE I—RENAL FUNCTION TESTS

Function	*Specific Measurement*	*Clinical Test*
Glomerular Filtration	Insulin clearance	Creatinine clearance Urea clearance Plasma urea level
Renal Plasma Flow	PAH clearance	PSP excretion
Proximal Tubule Mass	Excretory—TmPAH Reabsorptive—TmGlucose	PSP excretion —
Distal Tubule	Concentration—Dilution Electrolyte balance Acid-base balance Ammonia forming ability	
Severe Tubule damage and/or oliguria	(Back Diffusion)	Urea clearance Plasma urea level

at times is quite a close measure of the filtration rate,[9] but unfortunately the methods of analysis are not entirely specific and there may be considerable discrepancies. In congestive heart failure the creatinine clearance is usually significantly lower than that of inulin.[10] Nevertheless, the endogenous creatinine clearance represents the best simple routine estimation of filtration rate for clinical purposes. The urea clearance also depends in large part on the filtration rate, but is always lower due to passive back diffusion of urea thru the tubular epithelium. The back diffusion is variable and depends on the rate of urine flow,[11] the lower the urine flow the lower the urea clearance. As filtration rate falls below ⅓ of normal, there may be a progressive increase above the usually accepted normal values for plasma urea and non-protein nitrogen concentrations. But these levels can be modified by dietary intake as well as by the glomerular filtration rate, and thus a precise relationship between renal function and plasma urea level can not be established. Increases in plasma levels of substances such as inorganic phosphate and sulfate may also result from impaired filtration rate and may contribute to the development of acidosis and other symptoms.

PSP is excreted rapidly by the renal tubules[5] and, as the test is ordinarily performed, its excretion rate is probably a very crude reflection of the effective renal plasma flow in patients whose tubular function is not greatly impaired. Changes in the rates of glomerular filtration and

renal plasma flow can occur in the absence of structural damage in the kidneys. Glomerular hemodynamics are subject to a variety of physiological influences. Similarly, the ordinary clinical tests can indicate impaired renal function in the absence of organic kidney disease.

Glucose is most likely reabsorbed by the proximal convoluted tubules.[4] PAH presumably is also excreted by the proximal tubules. The maximum rates at which these substances are transferred by the renal epithelium are, therefore, reflections of the functional proximal tubular mass. These processes are also susceptible to functional controls, particularly hormonal. Since PSP is excreted by the renal tubules, its excretion rate may be influenced by tubular function as well as by renal plasma flow. When kidney damage is severe, the PSP excretion test is more dependent on tubular excretory mass than it is on plasma flow.

It is more difficult to assess distal tubular function in quantitative terms but it is probable that concentrating and diluting abilities are reflections of distal tubular activities. The ability of the kidneys to form ammonia is almost certainly a function of the distal tubules, as are probably a variety of other mechanisms concerned with acid-base and electrolyte balance.

There remains one other type of functional impairment to discuss. In the so-called "lower nephron nephrosis" there is actual necrosis of the renal tubular epithelium, which may follow a variety of chemical poisons or shock of various origins. There is anuria or oliguria and retention of nitrogenous products and other substances, which is due, at least in part, to back diffusion thru the inert tubular walls.[12] When oliguria is severe, even if only on a functional basis, the passage of urine down the distal tubules may be so slow that there is opportunity for greater than usual back diffusion of urea and electrolytes such as sodium and chloride, leading to a retention of these substances.

A very schematic representation of normal function is shown on the top line of Figure 1, glomerular function being indicated by the upper blocks, tubular function by the lower blocks. The kidneys are made up of approximately 2½ million units,[13] or nephra, each with a glomerulus and its attached tubule. These are represented by the row of similar units on the right. Some units are small and some are large. The important point, however, is that big glomeruli have big tubules, and small glomeruli are attached to small tubules. The summation, or average, of the individual units is shown by the larger figure on the left.

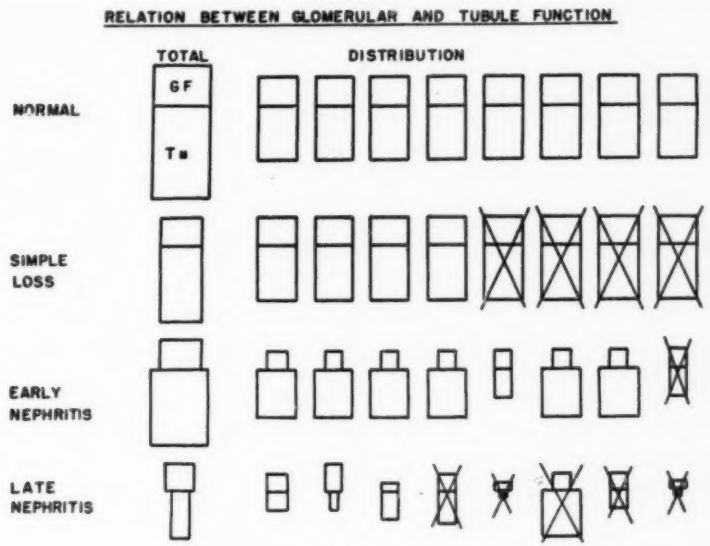

FIGURE 1

Simple loss of the renal tissue is represented on the next line—as if one kidney were removed, and before compensatory hypertrophy of the remaining kidney has developed. A similar situation probably arises in the arteriosclerotic kidney[14] where whole segments may be destroyed with no damage to other regions. Although total renal function may be considerably reduced, fairly normal relationship between glomerular and tubular function is usually preserved.

Various clinical tests of renal function, such as PSP excretion, and urea and creatinine clearances are below normal. Ability of the tubules to form ammonia as a defense against acidosis may also be reduced.[15] Although no symptoms are to be expected under ordinary circumstances, the kidneys in consequence of reduction in total function, are unable to respond with normal facility to situations of stress, such as surgical operations, shock and serious infections. Nitrogen retention develops more readily than in normals, as do acidosis and alkalosis.

There are more serious consequences where renal damage is such that an imbalance develops between glomerular and tubular function.

An example of this is shown on the third line—such as may occur in acute glomerulonephritis. In this instance, glomerular function, or filtration rate, is depicted as being half of the normal, as it was in the example of simple loss of renal tissue. Few or no units may be destroyed, but filtration rate is impaired more than tubular function[16] as measured by maximum ability to excrete PAH or reabsorb glucose. Further, all units may not be affected alike as indicated by the aberrant nephron. Sometimes it is possible to detect glomerular-tubular imbalance of this type by the use of ordinary clinical tests. Thus, the urea or creatinine clearances, which are rough measures of glomerular filtration rate, may be reduced relatively more than is the excretion of PSP, a substance whose excretion rate is dependent on renal plasma flow and tubular function.

Reduction in filtration rate, out of proportion to the reabsorptive capacity of the renal tubules for any particular substance, will tend to cause retention of that substance. This mechanism may contribute to the sodium retention and edema of acute nephritis. But it must be remembered that the renal tubules have a wide variety of functions to perform, not only reabsorptive and excretory but also synthetic. Even in a disease where glomerular damage appears to predominate, many observed abnormalities may be the result of damage to tubular function. Inability of the kidneys to concentrate and dilute as well as impaired ammonia formation in nephritis are undoubtedly due to tubular damage. These evidences of deranged function, probably of the distal tubules, may occur when proximal tubular function, as reflected by the maximum abilities of the tubules to excrete PAH or reabsorb glucose, show little or no impairment. Conversely, proximal tubular function may be considerably reduced with no evidence of abnormal distal function.

The advanced stages of any chronic renal disease are characterized by nitrogen retention. The clinical picture, however, may be quite variable, depending not only on the relative impairment of glomerular and tubular function but also on the degree to which the various tubular functions are affected. The situation, in regards to electrolyte balance, may be further complicated by involvement of extra-renal organs such as the heart and gastro-intestinal tract.

An example of terminal renal disease is shown on the bottom line of Figure 2. Many nephra are destroyed while the remaining units illustrate all possible combinations of glomerular and tubular impairment. Jean Oliver's beautiful dissections and reconstructions of diseased

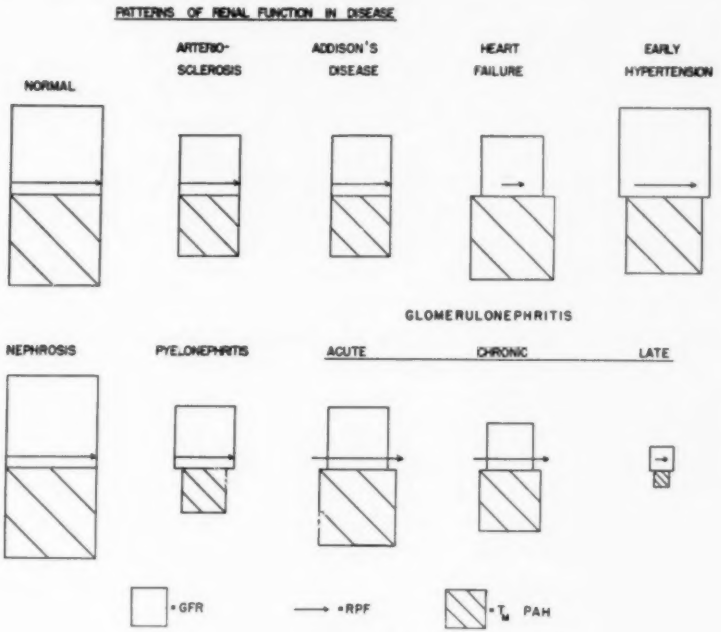

FIGURE 2

kidneys[17] indicate that the true situation may be more complicated, in that some parts of a single tubule may be hypertrophied while some parts are atrophied, and others may appear normal. Application of special techniques has also yielded functional evidence[7] that the chronically diseased kidneys may be made up of widely varying nephra, as illustrated in the figure.

Thruout the preceding discussion, the diagrams have been used as both anatomical and functional models. They are not, however, necessarily interchangeable. The tubular reabsorption of a number of electrolytes is subject to one or more different functional controls, chiefly hormonal, which may operate to produce abnormal electrolyte balance in the presence of completely normal kidneys. Reduction of glomerular filtration rate and renal blood flow may also occur on a purely functional basis.

In spite of the complex changes that may occur in the course of renal disease, a number of conditions are associated with fairly characteristic patterns of dysfunction. Some of these are illustrated in Figure 2. Again, glomerular filtration rate is indicated by the upper block and tubular function by the lower block. The arrow across the upper block represents the renal plasma flow. Thus, it is possible to visualize the relationships between these discrete renal functions. Normal functions and relations are shown by the diagram on the left. Maximum excretory capacity was chosen for this discussion since it is the tubular function that has been studied in the greatest number of diseases.

The first disease pattern is that of the arteriosclerotic kidney. As mentioned earlier, there appears to be simple loss of renal tissue in this condition and, although overall renal function may be considerably reduced, normal relationships between the several functions are preserved. Several observations[14,18] indicate that renal functions decline with advancing age but that again, fairly normal interrelations are preserved. Whether this is due to the development of renal arteriosclerosis or to some other factor in the aging process is not clear. In any case, it is unlikely that functional impairment in either of these conditions would be sufficient to be the sole cause of symptoms. This pattern of dysfunction is presented first, for it can complicate any other disease, renal or otherwise, occurring in the older age group.

An almost identical functional pattern is found in several endocrine disorders, most commonly in hypofunction of the anterior pituitary[19] and adrenal cortex.[20] It is likely that there is some atrophy of the kidney mass in these conditions, but some of the changes are functional in origin. In untreated Addison's disease, some of the reduction in renal function can be due to dehydration and shock, but adequate treatment with salt and Doca does not completely return the functions to normal.[21] Some recent experimental work[22] suggests that the growth hormone of the anterior pituitary may control kidney size and thus kidney function to some extent.

Another pattern, entirely functional in origin, has been described by a number of investigators[23,24,25] as being characteristic of congestive heart failure. Significant reduction in glomerular filtration rate is observed, sometimes to less than 50 per cent of normal. The striking change, however, is a marked decrease in renal plasma flow, leading to high filtration fractions, usually between 30 and 40 per cent in contrast

to the normal value of 19 per cent. Tubular mass, as measured by TmPAH or TmGlucose may be normal[26] or perhaps slightly reduced. Although the precise mechanisms responsible for the reduced filtration rate and renal plasma flow are not yet established, they are mostly functional in nature for return toward normal often occurs as congestive heart failure is relieved.[24,25,27-29]

A number of investigators[30,31] attribute the sodium retention of heart failure to the reduced load of sodium presented to the tubules in consequence of the lowered filtration rate. Although there is obviously an abnormal relation between the amount of sodium filtered at the glomerulus and the amount reabsorbed by the tubules, there are many factors operating on the tubules that may play a greater role in sodium retention than does the reduction in glomerular filtration rate.[29]

The functional pattern of essential hypertension[32] is also characterized by reduction in renal plasma flow. Filtration rate is relatively unaffected and there is a high filtration fraction. TmPAH is reduced, but not as much as is renal plasma flow. The ratio of filtration rate to TmPAH is usually high, that of plasma flow to TmPAH very low, indicating a relative renal ischemia. However, this renal ischemia is not the cause of the hypertension for all the renal functions may be normal in early cases of essential hypertension. As the disease advances there is actual destruction of renal tissue as evidenced by progressive impairment of filtration rate and TmPAH, but the renal ischemia and high filtration fraction persist, and the ratio of filtration rate to TmPAH remains high. Throughout the course of the disease TmGlucose and filtration rate maintain a normal proportional ratio.[7] Although renal function may eventually reach a very low level in the hypertensive kidney, death is usually the result of vascular complications in the heart or brain rather than the result of renal failure and except for the greater reduction of TmPAH, there does not appear to be glomerulo-tubular imbalance. Symptoms and signs due to kidney involvement are therefore rare. The development of hypertension in the course of chronic renal disease may obscure the functional pattern of the underlying disease.

The first diagram in the bottom line of Figure 2 is an example of a renal disease with a normal functional pattern. Although there have as yet been few reports on renal function in true or lipoid nephrosis, those available[33,34] indicate that all the usual kidney functions are normal, or even high normal. We have studied one patient with this disease

and repeatedly found that glomerular filtration rate, renal plasma flow and tubular excretory mass were normal.

The functional status of pyelonephritis has not been extensively studied. However, it appears[35,36] that renal plasma flow may be normal, may be high during febrile episodes or may be low following the development of hypertension or in advanced damage. Tubular function as measured by TmPAH suffers greater impairment than does glomerular activity. Distal tubular function is also involved in this disease, for the ability to form ammonia is frequently impaired with attendant chronic acidosis and loss of base through the kidneys. As a result, osteomalacia due to abnormal renal excretion of calcium and phosphorus, is a common complication of chronic pyelonephritis.[37] Loss of concentrating and diluting ability is another sign of distal tubular damage in this disease.

The characteristic finding in acute glomerulonephritis,[16,35,38,39] as would be expected from the histological picture, is reduction in glomerular filtration rate. The renal plasma flow, even in the presence of severe glomerular damage, is relatively normal, and in early acute nephritis may be greater than normal, indicating true renal hyperemia. The filtration fraction is generally low. Tubular function, as measured by TmPAH, may be unaffected in mild cases. If reduced, TmPAH is usually less involved than is glomerular function. Thus there is often a low filtration rate to Tm ratio. Glucose Tm is also relatively little affected in acute glomerulonephritis. This is not to say, however, that other tubular functions escape damage, for concentrating ability may be lost after several days, ammonia formation may be impaired, and there may be back diffusion of urea, electrolytes and other substances through damaged tubular walls.

The general functional pattern just outlined persists for some time as progressive kidney damage develops in chronic glomerulonephritis. Eventually, as the filtration rate falls to low levels, damage to the tubules outstrips glomerular impairment and the ratio of filtration rate to TmPAH reverts from a low value to normal and then to an abnormally high value. In the final stages of chronic nephritis, tubular excretory mass falls almost to zero.

One pattern of renal dysfunction will not be discussed fully. This is the shunting mechanism described by Trueta and his colleagues,[40] and which might possibly explain many aspects of kidney disorders.

TABLE II—RENAL FUNCTIONS IN ACUTE GLOMERULONEPHRITIS THAT HEALED

		IN		HO	
Phase	*Normal*	*Acute*	*Healed*	*Acute*	*Healed*
Time after onset	—	1 week	3 weeks	2 weeks	6½ months
Filtration Rate, ml/min	131	100	102	59	104
Renal Plasma Flow, ml/min	697	584	565	331	489
Filtration Fraction, %	19	17	18	18	21
TmPAH, mgm/min	77	—	—	42	82
TmGlucose, mgm/min	375	377	374	—	—
Urea clearance (% Ave. normal)	100	37	108	73	88

There is no doubt that these are most ingenious and brilliant observations and, although this phenomenon can be reproduced in experimental animals, evidence that this mechanism occurs in human disease is as yet highly controversial.

Although some of the patterns just described are fairly distinctive, it is well to remember that these diagrams simply depict the usual findings in the various diseases. Actually, there may be considerable overlapping and further, the natural histories of several of the diseases are quite complex. The remainder of this paper is devoted to a brief presentation of the findings in selected patients with glomerulonephritis and other diseases which illustrate various phases of diffuse renal disease.

Certain renal functions are shown in Table II for two patients with acute glomerulonephritis that healed. The normal values are taken from Goldring and Chasis.[41] Both were observed shortly after the onset of their acute nephritis, which in each instance followed a proven group A hemolytic streptococcal upper respiratory infection. At the time of the first observation, both had heavy proteinuria, microscopic hematuria and cylinduria, massive edema and hypertension. Glomerular dynamics were almost normal and TmGlucose was normal in IN, while filtration rate and TmPAH were approximately one half of normal in HO. However, all signs of renal disease disappeared by 3 weeks in patient

TABLE III—RENAL FUNCTIONS IN ACUTE GLOMERULONEPHRITIS THAT DID NOT HEAL

	CO			DA	
Phase	*Acute*	*Chronic*	*Chronic*	*Acute*	*Subacute*
Time after onset	3 months	1 year	5 years	1 week	5 weeks
Filtration rate, ml/min	107	138	109	55	36
Renal Plasma Flow, ml/min	1244	936	565	523	260
Filtration Fraction, %	8.6	15	22	11	14
TmPAH, mgm/min	82	94	96	—	—
TmGlucose, mgm/min	—	—	—	133	81
Urea Clearance (% Ave. normal)	74	101	—	50	29

IN and by 6½ months in patient HO. It might be noted that the greatest impairment of urea clearance was in patient IN who had an almost normal glomerular filtration rate. In 14 patients with acute glomerulonephritis, filtration rate averaged 55 per cent of normal with a range of 25 to 92 per cent, while tubular mass averaged 70 per cent of normal with a range of 36 to 128 per cent. In contrast to the example shown in Table II, the filtration fraction was low in 8 of the patients studied, the average being 13.

Although healing is the outcome in the majority of patients with acute glomerulonephritis, a small fraction die in the acute episode, while the remainder go into the chronic phase.[42] Two examples of this are shown in Table III. The clinical histories of these were similar to those shown in Table II. Although edema and hypertension were transient, proteinuria and hematuria did not disappear. The filtration fractions were characteristically low. The renal functions in patient CO were hardly below normal. Her functions were not observed until 3 months after the onset, but initially the urea clearance was 74 per cent of normal and the PSP was 70 per cent. At the end of 1 year, the renal functional pattern was normal although she definitely had chronic nephritis. However, her course was relatively benign in that the functions were still good 5 years after the onset. In contrast the course in DA is ominous. Four observations over a period of 5 weeks showed a progressive impairment in function and he should undoubtedly be

TABLE IV—RENAL FUNCTIONS IN CHRONIC GLOMERULONEPHRITIS

		BA		*BE*	*NA*
Phase	*Normal*	*Exacerbation*	*Chronic*	*Latent*	*Terminal*
Time after onset	—	4 years	5 years	1 year	years
Filtration Rate, ml/min	131	27	45	73	8
Renal Plasma Flow, ml/min	697	323	262	348	—
Filtration Fraction, %	19	8.3	17	21	—
TmPAH, mgm/min	77	29	44	—	2.7
TmGlucose, mgm/min	375	—	—	269	—
Urea Clearance (% Ave. normal)	100	21	30	54	—

classified as subacute. DA is the only one of the 14 patients with acute glomerulonephritis who showed this type of response. In these examples the urea clearance showed the functional trend very well. Unfortunately, there is as yet no way to predict which patient with acute glomerulonephritis will heal and which will become chronic. Serial observations of renal functions, however, are very useful in evaluating the clinical status of the patient.

Several phases of chronic glomerulonephritis are illustrated in Table IV. The exacerbation is a replica of the initial acute attack, but it is of considerable practical importance to distinguish between the two because of the different eventual prognosis. One clue as to whether or not an acute episode is an exacerbation or the initial attack is the length of the latent period between the preceding hemolytic streptococcal infection and the onset of renal signs. This period varies between 10 days and 4 weeks for the initial attack, and is usually 1 to 4 days for the exacerbation.[43,44] There is usually reduction of renal function in the exacerbation, with a pattern similar to that of the initial attack. This is illustrated by patient PA, who had had glomerulonephritis for 4 years and several previous exacerbations. One year after the exacerbation the functions showed definite improvement over those observed during the exacerbations, but never did approach normal. In most instances there has been no evidence that the exacerbation has caused permanent or progressive impairment of kidney function.

TABLE V—RENAL FUNCTIONS IN NEPHROTIC EDEMA

		FE	*SY*	*SN*	
Disease	*Normal*	*Glomerulo-nephritis*	*Amyloid*	*Nephrosis*	*Healed*
Filtration Rate, ml/min	131	25	45	125	122
Renal Plasma Flow, ml/min	697	173	397	708	679
Filtration Fraction, %	19	14	11	18	18
TmPAH, mgm/min	77	14	20	96	90
TmGlucose, mgm/min	375	179	—	—	—
Urea Clearance (% Ave. normal)	100	—	—	148	—

Patient BE, whose glomerulonephritis had persisted for one year, was in the latent phase with no symptoms and only moderate impairment of function. Again, without serial observations on kidney function. it is difficult to determine the rate of progress. Some patients with this degree of impairment may remain stationary for years, while others may deteriorate rapidly and die within a year. Patient NA whose functions were very low, died 3 months later. When functional impairment is this severe it is impossible to measure the renal plasma flow unless the extraction ratio is determined. There is nothing distinctive about the terminal phase, and in the absence of exact knowledge of the previous history, the diagnosis can only be made at autopsy, as in this case.

There remains one rather controversial phase of glomerulonephritis. Three instances of the nephrotic syndrome are given in Table V. Curiously, nephrotic edema is rarely if ever observed in nephrosclerosis or in pyelonephritis.[45] However, it is a common complication of chronic glomerulonephritis and of amyloid disease of the kidneys. When it occurs in these conditions, as illustrated by FE and SY, renal function is usually found to be considerably reduced and the pattern is that characteristic of glomerulonephritis with a low filtration fraction. Seven patients in the nephrotic phase of chronic glomerulonephritis had filtration rates ranging from 11 to 73 per cent of normal, tubular mass ranging from 9 to 74 per cent of normal, and filtration fractions were usually reduced. Several investigators[46] believe that glomerulonephritis whose clinical onset is characterized by the insidious development of

TABLE VI—RENAL FUNCTIONS IN HEART FAILURE AND ACUTE NEPHRITIS

		GR	*NI*	*HA*	
Disease	*Normal*	*Heart Failure*	*Acute Glomerulonephritis*	*Exacerbation and Heart Failure*	*3 months later*
Filtration Rate, ml/min	131	54	33	22	56
Renal Plasma Flow, ml/min	697	137	458	351	370
Filtration Fraction, %	19	39	7	6	15
TmPAH, mgm/min	77	—	34	41	41
Urea Clearance (% Ave. Normal)	100	64	29	13	44

proteinuria and edema represents a disease of different etiology than the hemorrhagic type of glomerulonephritis that follows group A hemolytic streptococcal infections. It is probable that some cases where the nephrotic syndrome is the first evidence of glomerulonephritis are simply instances where the initiating acute glomerulonephritis was so mild that the diagnosis was never suspected. However, there are so many instances of the nephrotic syndrome associated with impaired kidney function arising in patients for whom there is no evidence, clinical or bacteriological, of prior hemorrhagic glomerulonephritis, that a different etiology seems reasonable for some cases. Certainly, the intercapillary glomerular lesion of the Kimmelstiel-Wilson syndrome[47] associated with diabetes, impaired kidney function and nephrotic edema has a different etiology than the intra-capillary lesion of hemorrhagic glomerulonephritis. Incidentally, the functional pattern in several patients who probably have the Kimmelstiel-Wilson syndrome is indistinguishable from that of FE and SY in Table V.

Some investigators deny that there is such a disease as lipoid or "true" nephrosis, believing that it is a phase of chronic glomerulonephritis. Patient SN developed nephrotic edema at the age of 16, 3½ years before the observations on renal function shown in Table V. There was no hematuria and the blood pressure was always normal. In spite of the prolonged evidence of kidney disease, her renal function was completely normal. Shortly after these observations were made the

TABLE VII—RENAL FUNCTIONS IN MISCELLANEOUS DISEASES
(Normal Values are for females since these patients are female)

Disease	*Normal*	*FI* *Essential Hypertension*	*AR* *Disseminated Lupus*	*BA* *Kimmelstiel-Wilson*	*ST* *Unknown*
Filtration Rate, ml/min	117	60	42	40	64
Renal Plasma Flow, ml/min	594	277	698	199	—
Filtration Fraction, %	20	22	6	20	—
TmPAH, mgm/min	77	38	—	32	—
TmGlucose, mgm/min	303	—	262	131	178

syndrome spontaneously disappeared. Five years later she was again studied and her functions were almost identical to those obtained during the active phase of the disease. Not only the course of the disease, but also the functional pattern are quite dissimilar to ordinary glomerulonephritis.

Acute glomerulonephritis is sometimes complicated by congestive heart failure as well as by hypertension. Both these conditions are typically associated with a marked reduction in renal plasma flow and a high filtration fraction. Patient GR in Table VI is an example of congestive heart failure. The functional pattern of acute glomerulonephritis stands in sharp contrast, as illustrated by NI who had about the same degree of edema but no evidence of heart failure. Patient HA was studied shortly after the onset of an exacerbation in chronic glomerulonephritis which followed a hemolytic streptococcal infection. In spite of the complications congestive heart failure and hypertension, the functional pattern of an acute episode of glomerulonephritis predominated. Three months after the exacerbation and subsidence of the heart failure, the filtration rate had more than doubled, but there was no change in tubular mass or renal plasma flow.

Examples of the functional pattern in 4 other diseases with kidney involvement are given in Table VII. These patients are females, so normal values for their sex are indicated. The history of FI indicates the hypertension preceded any evidence of renal disease. However, there was heavy proteinuria and hematuria at the time the renal func-

tions were measured. Although there is impairment of filtration rate and excretory mass, indicating destruction of kidney tissue, the excessive reduction of renal plasma flow makes this the characteristic pattern of hypertension. AR, one of 2 patients with disseminated lupus studied, died 1 month after the observation shown in Table VII. In both patients tubular mass and renal plasma flow were in the normal range while the outstanding functional finding was a considerable reduction in filtration rate. BA had diabetes, slight hypertension, proteinuria, hematuria and edema. Although BA was not nephrotic, she probably represents an example of inter-capillary glomerulonephritis. ST, a 50 year old diabetic female, had normal urine and there was no reason to suspect renal disease. Three of 10 diabetic subjects selected at random, with normal urine, and no known renal disease had filtration rates ranging from 55 to 70 per cent of normal. It is not known whether this reduction in filtration rate is due to early arteriosclerosis, or inter-capillary glomerulosclerosis not yet sufficiently advanced to be accompanied by the fully developed syndrome.

Summary

The newer techniques for the measurement of discrete renal functions permit evaluation of glomerular and certain tubular functions in quantitative terms. Application of these measurements to the study of a variety of diseases affecting the kidneys has led to the establishment of a number of fairly characteristic patterns of renal dysfunction, both organic and functional in origin. Although the functional patterns at times may be of considerable diagnostic aid, their chief value lies in their guidance to an understanding of how disease processes can affect glomerular and tubular functions and their inter-relations. The natural history of diffuse renal disease is more meaningful if considered in relation to the changing patterns of dysfunction.

The ordinary simple clinical measurements of kidney function are less precise, but are useful, especially if their relations to specific renal functions are kept in mind.

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THERAPEUTIC RESULTS WITH AUREOMYCIN AND CHLORAMPHENICOL*

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THE two new streptomyces-derived antibiotics, aureomycin and chloramphenicol have greatly extended specific therapy in the group of infectious diseases. Within a brief period of eighteen months they have not only successfully combated certain important human infections caused by most gram-negative and a few gram-positive bacilli, but have shown themselves to be highly specific in all members of the rickettsial group and furthermore have significant effects on a few of the viral-like agents of disease. For purposes of brevity in this summary discussion a complete bibliography will not be given. Suffice it to say that many investigative groups have contributed to the ever-increasing knowledge of these two antibiotic substances.[1-4] It is noteworthy that the therapeutic results obtained have been amazingly similar, with certain notable exceptions, from the point of view of range of activity, specificity of action, uniformity of response and lack of significant toxic effects.

RICKETTSIAL DISEASES

Both antibiotics are strikingly effective in all experimental rickettsial infections. Results obtained in treatment of patients with Rocky Mountain spotted fever, scrub typhus, murine typhus and rickettsiapox are highly specific and similar. Indeed, there is rapid amelioration of the clinical symptoms with return of temperature to normal in about two days. Of equal significance is the ability of the antibiotics to exert favorable influence when started late in the course of disease. Chloramphenicol has been found effective in epidemic typhus fever, whereas aureomycin has proved of great benefit in patients with Q fever. Based upon the not yet complete clinical evidence it appears that each drug is equally effective in rickettsial infections. Treatment should be con-

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tinued until temperature has been normal for one day. Their mechanism of action is rickettsiostatic.

Gram-Negative Organisms

Major bacterial diseases of the Gram-negative group have been treated successfully. Chloramphenicol is unequivocally the drug of choice in typhoid fever. Our group (U.S. Army Scrub Typhus Team) studying this disease in Malaya has extended the original series of ten to approximately fifty cases and observed practically identical favorable results. Other investigators confirmed these findings. The typhoid patient improves within forty-eight hours, and the temperature returns to normal on an average of three and one half days. In the fifty above-mentioned patients there was a relapse rate of 53 per cent when treatment was less than eight days. Treatment for two weeks largely obviates this complication. Further studies are in progress. In spite of specific treatment, complications of hemorrhage and perforation have been observed. Our limited clinical results in other Salmonella infections are not as striking as in typhoid.

Both chloramphenicol and aureomycin appear to be equally effective in acute brucellosis of all types. Symptoms are promptly relieved and the temperature returns to normal in about three to five days. Relapses have occurred with either antibiotic, but the emergence of bacterial resistant strains is uncommon and re-treatment is equally beneficial. Reports of the use of combinations of antibiotics are appearing. Patients with proved chronic brucellosis are helped by treatment. Final evaluation of antibiotic treatment of brucellosis, a disease so variable in its clinical manifestations, is not yet possible, but the current results in the acute infection are very encouraging.

Various investigators report the favorable response of patients with tularemia to aureomycin in a manner comparable to that afforded by streptomycin. Unpublished work by members of our department (Parker, Lister et al) reveals that chloramphenicol is moderately beneficial in experimentally infected mice, and five human cases with tularemia have been effectively treated with this antibiotic.

The available data pertaining to experimental H. influenzae infections and in clinical meningitis caused by this organism is favorable to aureomycin. Additional unpublished data from our laboratory (McCrumb, et al) indicate that chloramphenicol is likewise effective. Mice experi-

mentally infected with H. influenzae are protected when chloramphenicol is introduced intramuscularly, and two infants ill with this disease rapidly improved.

Chloramphenicol has a wider range in chronic urinary tract infection because of its ability to combat P. vulgaris and P. aeroginosa. Otherwise, aureomycin and chloramphenicol are equally helpful in infections due to E. coli, A. aerogenes and K. pneumoniae. Certain diseases caused by Gram-negative cocci may be controlled. Various infections caused by meningococci have responded to aureomycin, but it is certain that this antibiotic will not supplant sulfonamides in this group. Chloramphenicol and aureomycin are effective in acute gonococcal urethritis. Each agent, however, is spirochestatic and, until their effect upon the Treponema pallidum is clear, these new antibiotics should be used with caution. Aureomycin has enjoyed more extensive testing in certain common streptococcal infections including those involving the endocardium. Although the results are favorable and additive, until more information is gained, penicillin is regarded as the drug of choice. Chloramphenicol has not been sufficiently tested in streptococcal infections.

Gram-Positive Infections

Patients with pneumococcal pneumonia have responded favorably to chloramphenicol and aureomycin. Additional clinical experience is needed to distinguish between their effects and to determine whether either drug is preferable to penicillin. Aureomycin is of proven benefit against staphylococcal infections and is of particular value when penicillin resistant strains have emerged.

Viral-Like Infections

The reported *clinical* experience with these antibiotics in viral-like infections is limited largely to the effect of aureomycin in diseases of the psittacosis-lymphogranuloma group. The available data are favorable but not spectacular in lymphogranuloma venereum. Patients with psittacosis have responded rapidly to aureomycin.

Three independent groups of observers detail the favorable response of patients with primary atypical pneumonia to aureomycin. Our results with chloramphenicol are similar. Nevertheless, this syndrome of suspected virus etiology is difficult to assess. Efforts toward specific

etiology are to be emphasized. Therapeutic effects obtained in patients with measles, mumps, herpetic virus diseases and infectious mononucleosis are inconclusive, although the results invite further clinical testing. There is no evidence of benefit derived from these antibiotics when employed in other viral infections.

Dosage and Toxicity

For most acute infections the following doses are recommended: (1) Chloramphenicol, initial dose of 50 mg./kilo and daily dose of 50 mg./kilo given in 4,6 or 8 hour intervals; (2) Aureomycin, initial dose of 25 mg./kilo body weight and daily dose of 25 mg./kilo given in 4,6 or 8 hour intervals.

In general it may be safely stated that both of these antibiotics from streptomyces are well tolerated by human beings without significant ill effects. Nevertheless, the promiscuous use of either agent without clear-cut indication is ill-advised.

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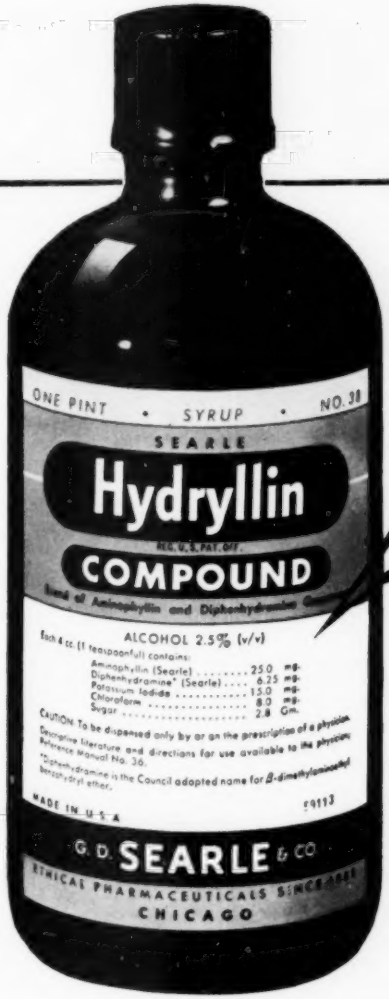
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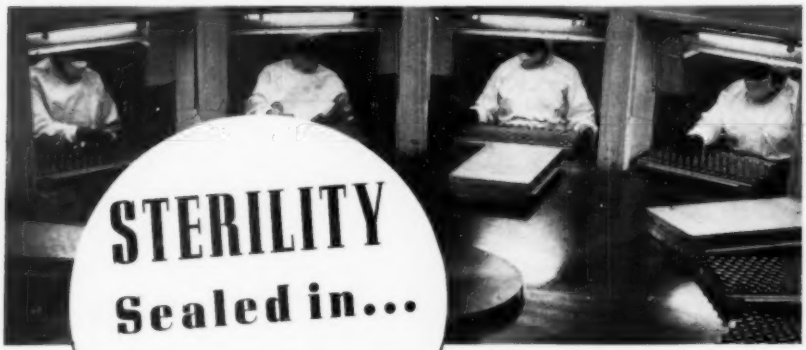

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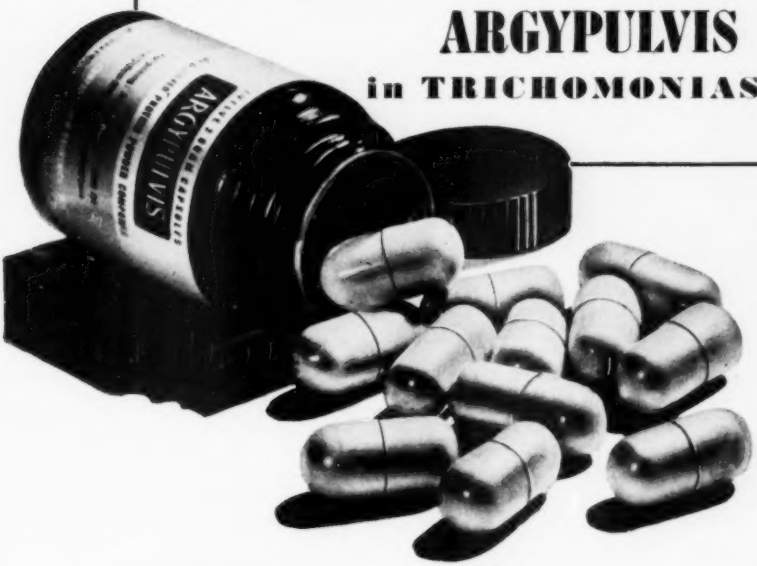

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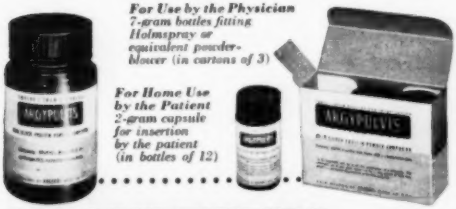

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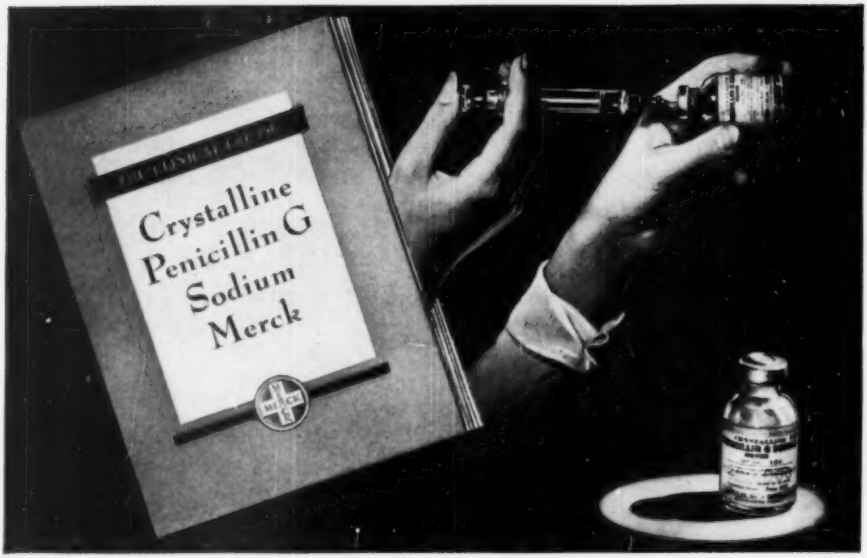

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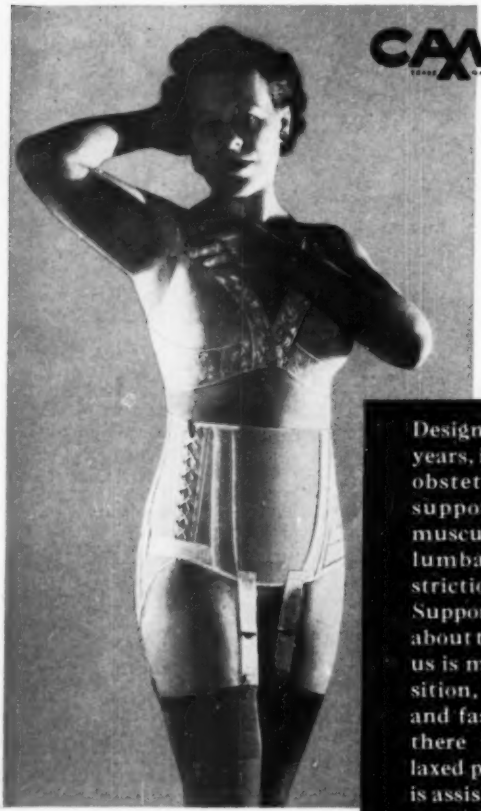

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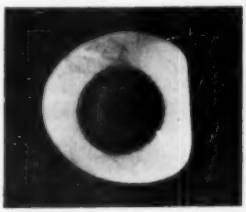

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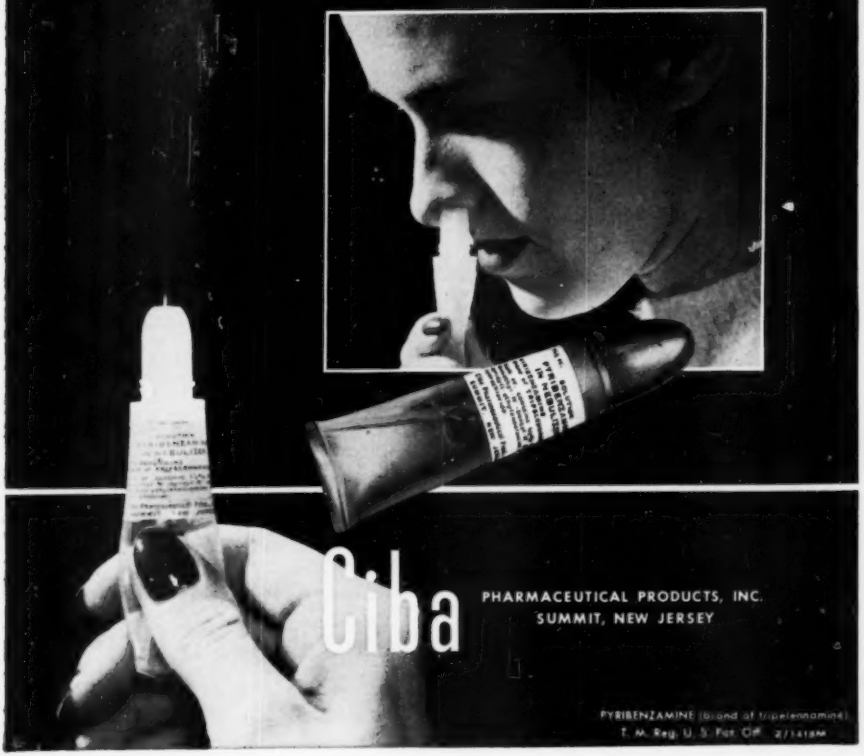

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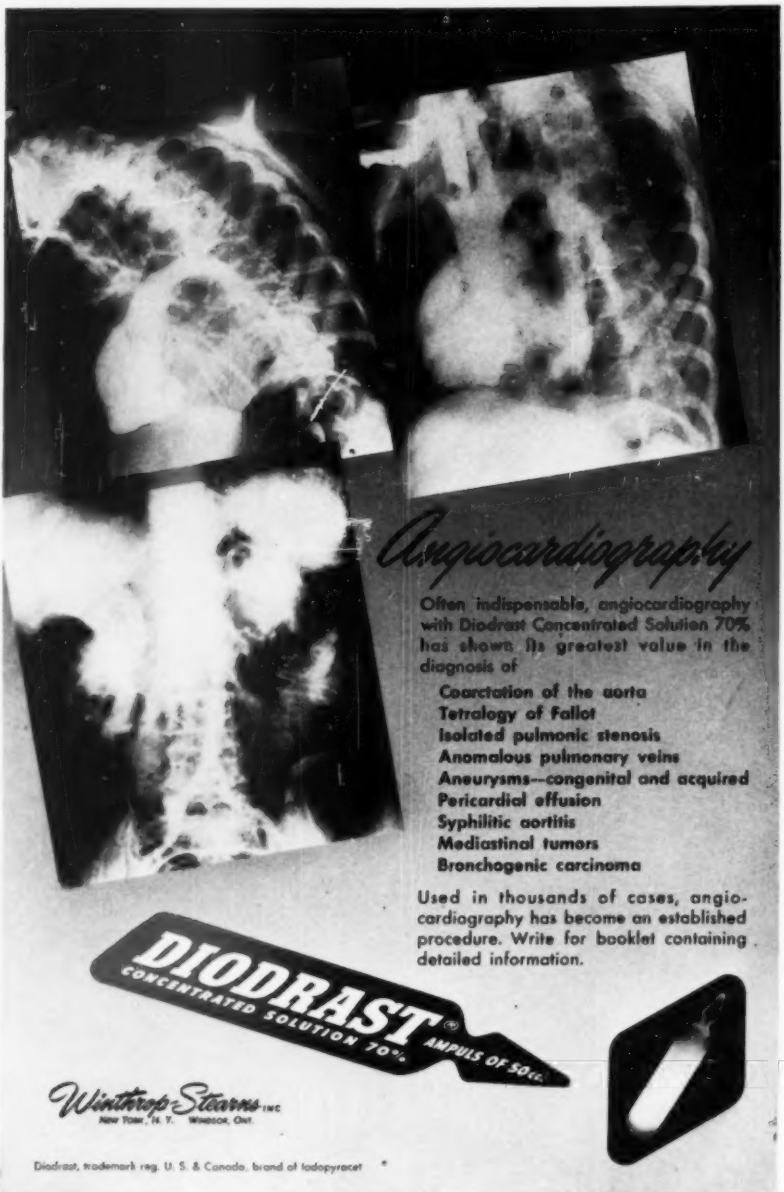
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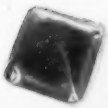

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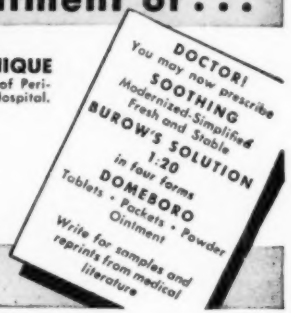

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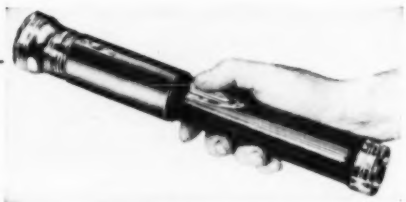

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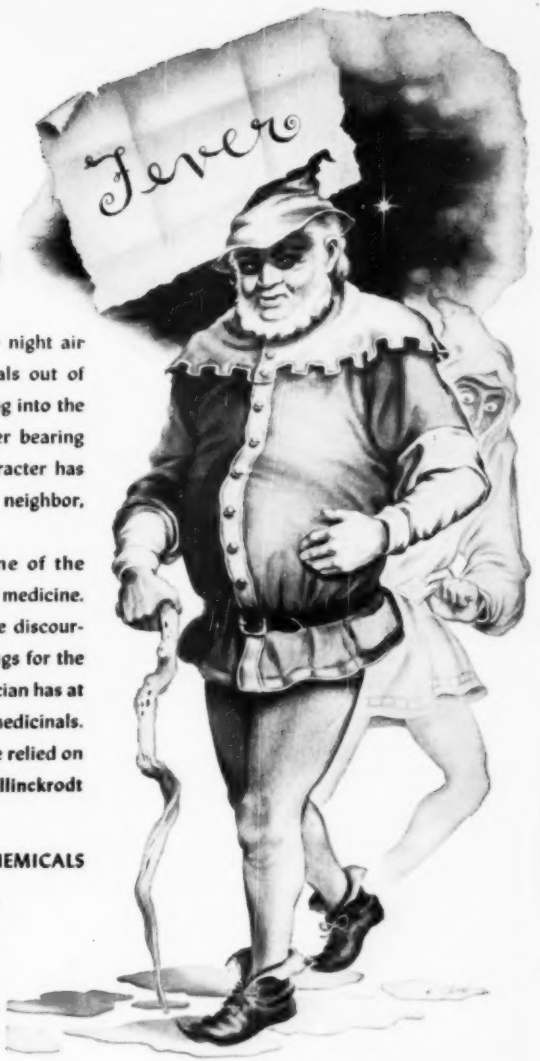

An unsuspecting villager braves the night air for a stroll. A slinking stranger steals out of the shadows and slyly slips something into the stroller's pocket . . . a scrap of paper bearing one word: "Fever." The sinister character has shamelessly wished his fever on his neighbor, believing thus to rid himself of it.

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